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PRESIDENTIAL ADDRESS

Dr. Barun Kumar Nayak

Thanks, Dr Mahipal for the lovely introduction.

Our Chief Guest Honorable Mr Anil Baijal, Lt Governor of Delhi, Dr Mahipal, Immediate Past President, Respected Seniors, Colleagues and Friends, First of all I am thankful to Honorable Mr Baijalji for sparing time for us, specially considering the Covid 19 pandemic situation. Taking over as your President I am thankful to all of you for showing faith in me and electing me to this position. Your love and appreciation showered on me through the years has been the driving force for me to work hard.

When I look back at the list of past Presidents, it gives me a wonderful feeling to be standing in line with some of the legends and stalwarts in the field of Ophthalmology, I truly feel humbled. I wish my parents were present here to watch the joy in me, but they are not in this world now and must be showering their blessings from heaven. My life’s journey has not been very different from that of many of you and I am sure that many like me have faced difficult times in their lifetime. I thank the Lord for having chosen me to be born to my parents as I truly feel that had it not been for their simple ideology I would have never been able to have a fulfilling journey in life.

Their ideology was as simple as it could get – lead a life where you do the right thing which keeps your conscience clear, don’t compromise on your ethics and give each and everything that you are supposed to do your best shot without any short cuts. These and similar statements that fell on my ears through my growing years groomed me into the person that I am today.
I am an AIOS member for more than 37 years and have been actively involved in AIOS since 1995 in various capacities and through all my positions, I have worked only and only with one intention which is for the benefit of AIOS and its members. I have had the honor of having AIOS stalwarts as my teachers. I have seen them work selflessly and have taken inspiration from them. Each time I have had to make a strong decision in whichever position, I kept the legacy of AIOS in mind and acted accordingly. I know from the deepest part of my heart that there has not been a single incidence where I have compromised on the integrity of the AIOS office.

Today when my journey has culminated to this point in life where I stand before you, as President of AIOS, I feel that I have a huge responsibility to carry on my shoulders. Having said that, let me assure you that this responsibility is most welcome because I know that it is only through this office and position that once again I can do some thing fruitful and tangible for this institution.

You all have supported me whether as Editor-IJO or as Hony. Secretary AIOS and I look forward to the same confidence and support from you today as I take up this new prestigious position. I know that we are missing out on our annual physical AIOS conference which is the culmination of the efforts of the entire AIOS office at the end of the year.

However, today it is our responsibility to see that we do our best in this pandemic and in the given restrictive circumstances, avoid gatherings and respect the protocols of social distancing. Thankfully we are blessed with a fantastic social media and we find ourselves connected today over the internet. Though I miss being at close proximity with you all I
would never want to compromise on your safety and hence I am happy to connect with all of you digitally.

Many people ask me about my plan for the year. However, I have a vision which will have a long term implication for the years to come. We have grown to become the largest society of ophthalmologists of life members in the world. Hence the most needed action required is to further streamline the working of our Institution. Streamlining any organization only ensures smooth operation and transparency which is utmost for any society to progress.

Today I consider that I am fortunate to represent you all and see myself as your proxy. I personally feel that the society belongs to its members and not just a handful of people who hold office. Membership is growing very fast and majority are in smaller towns or remote places. I want to give confidence to all in believing that it is not an “exclusive” for a select few but an “inclusive” society for all. I would like you all to voice your opinion and share suggestions and ideas for the benefit of the society.

However, I request you to study and research by going deep in your idea. Consider and reconsider it, question it, discuss it amongst your groups, look for facts and figures to support it. You must ensure before sending it to my office that it is fully detailed and that it is going to benefit the society at large and not just a handful of people. I promise you today that any idea which is for the benefit of the society will be considered and discussed in the relevant committee and if it proves to be beneficial to AIOS, I will put in all efforts so that your suggestion is adopted.
It is almost a year and a half that we have been going through the pandemic. Though things and understanding of the situation is improving as days pass by we cannot undermine the havoc caused in the lives of many because of it. Whether big cities or small towns every single household has been affected because of the Corona virus. People are facing financial lows, social isolation leading to lack of communication have made long lasting impressions on all.

Though the situation is not going to get better overnight, I plan to take steps towards improving it from the point of view of our own members. I will try to handle the concerns and problems of AIOS members specially from the smaller places, in relation to the pandemic and help them to find solutions to it.

My major concern which I want to address is to build a robust scientific program so that more and more delegates are encouraged to attend the conference. Although we are adding more than a thousand new members every year, since the past six years if we look at the attendance in the annual conference which is not improving. I have come to this conclusion based on certain observations.

The number of ophthalmology delegates from the conference of 2017 is shown in this graph. This graph is showing the number of speakers in each conference since 2017. Hence we can deduce from these figures number of delegates minus number of speakers, are the ones who are really attending the conference to get benefitted from the scientific program are decreasing. On top of it there has been a constant rise in the number of halls since 2014 which has resulted in thinner attendance in each hall.
I will request the Scientific Chairman to look into this matter seriously and sincerely in consultation with the scientific committee members and GC members that how the scientific program can be modified so that more doctors would be attracted to attend them thereby increasing the participation from the delegates. I will be always available in whatever way I can contribute towards this effort.

I firmly believe that for any society to run smoothly and progress, a sound financial base is of utmost importance. The base should be such that even if the society does not have any addition to its treasury for 3 consecutive years, like during the Corona pandemic, it should have the capacity to survive. The logic behind this is very simple – Growth always depends on a strong financial background. We must ensure that any amount of money that is spent, is spent judiciously and we must maximize that value of that money.

Just to prove the point, as Editor IJO I could generate Rs.4.75 crores surplus during my tenure and hand it over to the next Editor so that he would not face any problems after taking over. Similarly, when I became Secretary of AIOS, the AIOS HQ had a balance of Rs.20 crore approx. which almost doubled to Rs.39 crore at the end of my tenure of three years. Hence, I would urge all units of AIOS to work with this philosophy.

Review and modification of the AIOS constitution is also on my agenda to be considered. Dr Babu Rajendran also tried to work on this in 2008 wherein I was also involved as Editor IJO. Since then it is hovering in my mind and I will make sincere efforts to achieve this within the framework of law.

I completely agree to the views put forth by Retd Field Marshal Sam Maneckshaw, that leaders are not born. Anyone with reasonable common sense, decency, passion and a
strong desire to achieve, along with sound professional knowledge and competency can be a good leader. Before signing off, I would like to take the liberty of advising young ophthalmologists not to let just money be your driving point. The one thing that you should never compromise on is your ethics. Apparently, money is never enough and the only sure-shot way to ensure that your night sleep after a hard day is sound, is to have a clear conscience. A litmus test for it would be when your own conscience assures you of that and you feel appreciated and contented from within.

Long Live AIOS
EDITORIAL ADDRESS

Editor Proceedings Report - AIOC 2021

Dr. Arup Chakrabarti

Dear Esteemed Colleagues

Greetings from the Desk of Editor Proceedings (EP) AIOS

Activities for the Year 2021

As you all know we had made a conscious effort to go paperless for the entire gamut of activities of editor proceedings and hence most of our efforts have been focused on developing and upgrading the Proceedings Website contents and on biweekly emails carrying scientific contents presented at the AIOC 2021.

Proceedings website :

The annual AIOC 2021 was a virtual conference this year and the Team scientific committee has done a very good job - it was a virtual academic feast. As the Chairman Scientific Committee had mentioned about 500 programs were running in all the virtual halls. These programs were actually not planned to stream live in any other channel in accordance with the OBSC decision. It was felt that this strategy of deferring the live streaming of the meeting deliberations will result in a higher number of registrations. Editor Proceedings team had received links for all the scientific presentations on a daily basis from the AV team engaged by the AIOS secretariat. Team Editor Proceedings have downloaded the contents. The downloaded contents have been processed and rendered suitable for utilization in the future. We have done away with the earlier practice of receiving copies of the downloaded contents in multiple hard disc drives. Since a huge quantum of data is involved it would have required 40 to 50 hard disk drives with an implication of cost escalation, additional processing time with the unfortunate chance of data loss due to HDD crash.
We had fast tracked the activities. The AIOS office has extended full co-operation in this venture.

If you visit the website you will find abstracts of all the submitted sessions. The proof-read texts of the best paper of the sessions have also been uploaded. In compliance with the OBSC decision like in 2020 this year too there will be no hard copy of the AIOS Best Papers Proceedings book. This decision was taken in view of the financial crunch that the AIOS is going through. The soft copy has been uploaded on the website. All the e-posters, physical posters have been converted to web format and embedded there. The site also contains all the presented videos. The bi weekly mailers which go up to 24000 plus AIOS members are also archived in the communication page of the website. We received about 24 TB of data after the 2021 conference and though it was quite humongous amount of data - it was crunched and ultimately, uploaded - 3716 videos on the YouTube channels of the editor proceedings. 3444 videos were also embedded on the website. The volume has actually increased by 35.5 percent from the previous year. The website has become quite popular and everyday it attracts about 685 visitors. Total unique visitors recorded over the last year has been 21475. The user base has increased significantly. 89 percent of visits are from India. As I have mentioned earlier we have three YouTube channels and there are 9770 followers on the primary channel which is an increase by 16% compared to the previous year. A renewed request is made to the AIOS president to involve the Editor Proceedings in the discussions while finalizing the AV vendor. This will go a long way in preventing the recurring recording mistakes that have been happening at the AV end. The AV team also has to be instructed to meticulously follow the recording guidelines prepared by me and repeatedly submitted by me to the AIOS secretariat. Poor quality recording cannot be enhanced for a better viewer experience.

**Mass emails:** We have also embarked on the mass email campaign for the last couple of years and this year so far, we have sent out about 90 mass emails to more than 24000 ophthalmologists across the country.
This activity too has been found to be very useful and popular by all sections of ophthalmologists in the country.

Members of AIOS particularly the younger ophthalmologists do write to me or call me expressing their happiness over this mode of knowledge distribution. Over 6,09,482 email reads have been noted.

**Activities for the Virtual AIOC 2022**

I would like to thank the outgoing President Dr. Barun Nayak for his wonderful tenure and complete support in my endeavors. He has been responsible for raising the bar for all facets of AIOS activities. I would like to welcome our incoming President Dr. Lalit Verma and wish him all the best in his effort to further improve the performance of All India Ophthalmic Society. My thanks are also due to the headquarters, Secretary, Treasurer and support staff of AIOS headquarters, the AV team, and last but not the least the people from Numerotec who have done exceptionally good work in getting us to work at a very efficient level.

I will be getting in touch with you at frequent intervals for updates.

Please don't hesitate to contact me for any queries. Let us all work together to take AIOS to greater heights.

Best Wishes

Yours Sincerely

**Dr. Arup Chakrabarti**

editorproceedings@aios.org
Best Free Paper Awardees

AIOS – Sante Vision Award (Cataract) - Dr. Rajendra Prasad (P14714) – Sewing Needle Micro Capsulotomy: New Technique To Prevent Argentinian Flag Sign

AIOS - Community / Social Ophthalmology Award - Dr. Praveen Vashist (V11693) - National Survey For Mapping Human Resource & Infrastructure For Eye Care Services In India

AIOS - Comprehensive Ophthalmology Award - Dr. Kirti Singh (K04958) - Phase 1/2 Study Of Intravitreal Gene Therapy For Vision Restoration In Advanced Retinitis Pigmentosa

AIOS - Cornea Award - Dr. Ritika Mullick (R23525) – Next Generation Crosslinking (Cxl) Calculator For Titration Of Energy In Thin Keratoconic(Kc) Cornea

AIOS – Rema Mohan Award - Dr. Poornachandra B (P14831) - Comprehensive Approach And Exploring Therapeutic Potentials In Retinal Dystrophies

AIOS - K.C. Singhal Award - Dr. Bidisha Mahapatra (B20295) - Infectious Scleritis: Changing Profile In A Tertiary Eye Care Centre

AIOS - K.C. Singhal Award - Dr. Madhushmita Mahapatra (M22861) - Novel Technique Of Sutureless, Glueless Amniotic Membrane Grafting In Acute Stevens Johnson Syndrome

AIOS – D B Chandra Disha Award - Dr. Nikhil Balakrishnan (B20247) - Deciphering The Conundrum Of Aerosolisation During Non Contact Tonometry (Nct)

AIOS - Lacrimal Award - Dr. Gaurav Garg (G19074) - Outcomes Of Inferior Turbinate Tarsal Infracture For Congenital Nasolacrimal Duct Obstruction
AIOS – S D Athawale Award - Dr. Harshavardhan Ghorpade (G14398) - Artificial Intelligence And Wolfram Language In Papilloedema

AIOS - Ocular Pathology / Ocular Oncology and Tumors Award - Dr. Akshay Nair (N12639) - Orbital Mass As Presenting Sign Of Underlying Malignancy: Clinical, Pathological Features & Outcomes

AIOS - Optics / Refraction / Contact Lens - Dr. Venkataprabhakar Guduru (G18472) - Anti Dysphotopsia Lens – A Novel Intraocular lens Design To Prevent Dysphotopsia Post Cataract Surgery

AIOS – Sujatha Savitri Rao Award - Dr. Gagan Dudeja (D08805) - Epithelial To Mesenchymal Transition In Retinoblastoma Tumors: A New Target?

AIOS - Om Prakash Award - Dr. Tanvi Gaonker (T23161) - Retropupillary Iris Claw Lenses Versus Scleral Fixated Lenses In Children With Large Subluxations

AIOS – Shiv Prasad Hardia Award - Dr. Pooja Khamar (K17849) - Next Generation Rapid Tear Diagnostic Kit For Refractive Surgery.

AIOS – Prem Prakash Disha Award - Dr. Sayali Mahajan (S19692) - Botulinum Toxin Augmented Strabismus Surgery In Large Angle Esotropia- Saviour In Disguise.

AIOS - Trauma Award - Dr. Sangeet Mittal (M09477) - Chorioretinectomy For Deep Impact Ocular Trauma In Indian Eyes

AIOS – Narsing A Rao Award - Dr. Vivek Dave (D12385) - Comparative Outcomes In Endophthalmitis Caused By Biofilm Positive And Biofilm Negative Bacteria

AIOS – S Natarajan Award - Dr. Tapas Ranjan Padhi (P19272 ) - Can Rate Of Vascular Outgrowth Be A Predictor For Treatment In Babies With Rop?
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Comparative Analysis Of Visual Outcomes Of A New Non-Diffractive Extended Vision Intraocular Lens’

Dr. Nidhi Gajendragadkar

INTRODUCTION

• Standard monofocal IOLs can give good distance and corrected near vision, but poor intermediate vision.
• Multifocal IOLs give spectacle independence for near but can have decreased contrast sensitivity and photic phenomenon.
• With the arising need for better intermediate vision, Extended depth of focus IOLs have been introduced, but they can also be associated with photic phenomenon.

TECNIS ZCB00 IOL (JOHNSON & JOHNSON VISION CARE, INC.)

• Single piece 6.0 mm biconvex hydrophobic acrylic monofocal IOL
• Aspheric anterior surface
• Negative spherical aberration of 0.27 μm
• Frosted, continuous 360 degree posterior square edge
EYHANCE ICB00 IOL (JOHNSON & JOHNSON VISION CARE, INC.)

- Newly developed Monofocal IOL
- Same features as the ZCB00 IOL & visually indistinguishable
- Additionally ICB00 has a modified aspheric anterior surface of the optic
- Creates a continuous power profile

(The power increases continuously from the periphery to the center of the lens)

- Aims at improving vision for intermediate tasks compared with a standard monofocal IOL & extend the depth of focus
- It is based on the refractive technology, without diffractive rings and without zones.

PURPOSE

To compare a new non-diffractive Extended vision IOL Eyhance ICB00 with the Standard Monofocal IOL Tecnis ZCB00 (Johnson & Johnson Vision Care, Inc.)
METHODS

- Prospective non-randomized comparative study
- Single surgeon
- Tertiary care eye hospital
- Data analysed with SPSS software. Version 20
- p value < 0.05 considered significant

![Group 1 and Group 2](image)

INCLUSION CRITERIA

- Age 50 to 75 years
- Corneal astigmatism =/< 0.75D
- Endothelial cell count > 2000 cells/mm2
- IOL implanted 20.00 - 23.50 D
- In the bag IOL

EXCLUSION CRITERIA

- Previous trauma/intraocular surgery
- Irregular astigmatism
- Corneal dystrophy/scar
- History of Glaucoma/intraocular inflammation
- Macular disease/retinopathy
- Neuroophthalmic diseases
- Intra/post-operative complication
Outcome measures were calculated at 90 days.
Visual acuity was taken with logMar charts for distance, intermediate (60 cm) and near (40 cm).

RESULTS

DISTANCE VISUAL ACUITY

Distance vision shows comparable results between (Gr-1) & (Gr-2). Difference is non-significant. (p = 0.13).

Group statistics

<table>
<thead>
<tr>
<th>SL NO</th>
<th>N</th>
<th>MEAN</th>
<th>STD. DEVIATION</th>
<th>STD.ERROR MEAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>UDVA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Gr-1)</td>
<td>50</td>
<td>0.099</td>
<td>0.12677</td>
<td>0.01793</td>
</tr>
<tr>
<td>(Gr-2)</td>
<td>50</td>
<td>0.050</td>
<td>0.05051</td>
<td>0.00714</td>
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</tbody>
</table>

T test for equality of means

<table>
<thead>
<tr>
<th>T</th>
<th>df</th>
<th>Pvalue</th>
<th>Mean Difference</th>
<th>Std. Error Difference</th>
<th>95% Confidence Interval of the Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>98</td>
<td>0.13</td>
<td>-0.25340</td>
<td>0.03165</td>
<td>-0.31622 - -0.19058</td>
</tr>
</tbody>
</table>

-8.005
INTERMEDIATE VISUAL ACUITY (60CM)

Intermediate visual acuity (60 cm) shows UIVA is significantly better in Group 1 (ICB00) (p = 0.000).

Group statistics

<table>
<thead>
<tr>
<th>SL NO</th>
<th>N</th>
<th>MEAN</th>
<th>STD. DEVIATION</th>
<th>STD.ERROR MEAN</th>
</tr>
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<tr>
<td>(Gr-1)</td>
<td>50</td>
<td>0.2524</td>
<td>0.05490</td>
<td>0.00776</td>
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<tr>
<td>(Gr-2)</td>
<td>50</td>
<td>0.5058</td>
<td>0.21699</td>
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T test for equality of means

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<th>df</th>
<th>P value</th>
<th>Mean Difference</th>
<th>Std. Error Difference</th>
<th>95% Confidence Interval of the Difference</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>-8.005</td>
<td>98</td>
<td><strong>0.000</strong></td>
<td>-0.25340</td>
<td>0.03165</td>
<td>-0.031622</td>
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</tbody>
</table>
NEAR VISUAL ACUITY (40 CM)

Uncorrected Near Visual Acuity for (Gr-1) & (Gr-2) is Comparable
Difference is non-significant (p = 0.60).

Group statistics

<table>
<thead>
<tr>
<th></th>
<th>SL NO</th>
<th>N</th>
<th>MEAN</th>
<th>STD. DEVIATION</th>
<th>STD.ERROR MEAN</th>
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<tbody>
<tr>
<td>UNVA</td>
<td>(Gr-1)</td>
<td>50</td>
<td>0.4512</td>
<td>0.20839</td>
<td>0.02947</td>
</tr>
<tr>
<td></td>
<td>(Gr-2)</td>
<td>50</td>
<td>0.5176</td>
<td>0.13300</td>
<td>0.01881</td>
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T test for equality of means

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<th>Df</th>
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<th>Std. Error Difference</th>
<th>95% Confidence Interval of the Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-1.899</td>
<td>98</td>
<td>.060</td>
<td>-0.06640</td>
<td>0.03496</td>
<td>Lower [-0.13578] Upper [0.00298]</td>
</tr>
</tbody>
</table>

- Uncorrected Distance and Near visual acuity show comparable results between (Gr-1) & (Gr-2).
  Difference is non-significant. (p = 0.13 and p = 0.60 respectively).
- Uncorrected Intermediate visual acuity (60 cm) is significantly better in Gr-1 (ICB00) (p = 0.000).
<table>
<thead>
<tr>
<th>PHOTOPIC</th>
<th>No. of eyes</th>
<th>5 CPD Mean SD</th>
<th>10 CPD Mean SD</th>
<th>15 CPD Mean SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr -1</td>
<td>50</td>
<td>0.832</td>
<td>0.03</td>
<td>0.62</td>
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<td></td>
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<td>3</td>
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<td>81</td>
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<td></td>
<td></td>
<td>0.837</td>
<td>0.02</td>
<td>0.62</td>
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<tr>
<td></td>
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<td>5</td>
<td>44</td>
<td>66</td>
</tr>
<tr>
<td>Gr -2</td>
<td>50</td>
<td>0.604</td>
<td>0.04</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
<td>51</td>
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<td></td>
<td></td>
<td>0.606</td>
<td>0.04</td>
<td>0.35</td>
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<td>2</td>
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<td>58</td>
</tr>
<tr>
<td>90 days</td>
<td></td>
<td>0.699</td>
<td>0.047</td>
<td>0.699</td>
</tr>
<tr>
<td>Gr -1</td>
<td>50</td>
<td>0.709</td>
<td>0.034</td>
<td>0.709</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>99</td>
<td>16</td>
</tr>
<tr>
<td>Gr -2</td>
<td>50</td>
<td>0.352</td>
<td>0.044</td>
<td>0.352</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
<td>8</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.356</td>
<td>0.044</td>
<td>0.356</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>5</td>
<td>87</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MESOPIC</th>
<th>No. of eyes</th>
<th>5CPD Mean SD</th>
<th>10 CPD Mean SD</th>
<th>15 CPD Mean SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 days</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Gr -1</td>
<td>50</td>
<td>0.699</td>
<td>0.047</td>
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<tr>
<td></td>
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<td>0.709</td>
<td>0.034</td>
<td>0.709</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.356</td>
<td>0.044</td>
<td>0.356</td>
</tr>
<tr>
<td>Gr -2</td>
<td>50</td>
<td>0.352</td>
<td>0.044</td>
<td>0.352</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.356</td>
<td>0.044</td>
<td>0.356</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>5</td>
<td>87</td>
</tr>
</tbody>
</table>
## MODULATION TRANSFER FUNCTION

Gr-1 (ICBOO) Vs Gr-2 (ZCBOO) T TEST

<table>
<thead>
<tr>
<th>Photopic condition</th>
<th>t</th>
<th>df</th>
<th>P value</th>
<th>Mean Difference</th>
<th>Std. Error Difference</th>
<th>95% Confidence Interval of the Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>5CPD</td>
<td>7  DAYS</td>
<td>0.469</td>
<td>98</td>
<td>0.64</td>
<td>0.0038</td>
<td>0.0082</td>
</tr>
<tr>
<td>90 DAYS</td>
<td>0.494</td>
<td>98</td>
<td>0.623</td>
<td>0.0034</td>
<td>0.0068</td>
<td>-0.01009</td>
</tr>
<tr>
<td>10CPD</td>
<td>7  DAYS</td>
<td>0.494</td>
<td>98</td>
<td>0.623</td>
<td>0.003340</td>
<td>0.006767</td>
</tr>
<tr>
<td>90 DAYS</td>
<td>0.171</td>
<td>98</td>
<td>0.865</td>
<td>0.00152</td>
<td>0.008909</td>
<td>-0.01616</td>
</tr>
<tr>
<td>15 CPD</td>
<td>7  DAYS</td>
<td>0.186</td>
<td>98</td>
<td>0.852</td>
<td>-0.00152</td>
<td>0.00815</td>
</tr>
<tr>
<td>90 DAYS</td>
<td>0.404</td>
<td>98</td>
<td>0.687</td>
<td>0.00362</td>
<td>0.00896</td>
<td>-0.01416</td>
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</table>

In Photopic Conditions, no statistical difference between Gr-1 vs Gr-2 at 7 & 90 days.
<table>
<thead>
<tr>
<th>Mesopic condition</th>
<th></th>
<th>t</th>
<th>df</th>
<th>P value</th>
<th>Mean Difference</th>
<th>Std. Error Difference</th>
<th>95% Confidence Interval of the Difference</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>t-test for Equality of Means</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5CPD 7 DAYS</td>
<td>0.459</td>
<td>98</td>
<td>0.647</td>
<td>0.0042128</td>
<td>0.009183</td>
<td>-0.01403 to 0.022451</td>
<td></td>
</tr>
<tr>
<td>5CPD 90 DAYS</td>
<td>0.441</td>
<td>98</td>
<td>0.66</td>
<td>0.00412</td>
<td>0.009347</td>
<td>-0.01443 to 0.022669</td>
<td></td>
</tr>
<tr>
<td>10CPD 7 DAYS</td>
<td>1.2</td>
<td>98</td>
<td>0.233</td>
<td>0.01004</td>
<td>0.008369</td>
<td>-0.00657 to 0.026648</td>
<td></td>
</tr>
<tr>
<td>10CPD 90 DAYS</td>
<td>0.354</td>
<td>98</td>
<td>0.724</td>
<td>0.00316</td>
<td>0.008928</td>
<td>-0.01456 to 0.020878</td>
<td></td>
</tr>
<tr>
<td>15CPD 7 DAYS</td>
<td>0.385</td>
<td>98</td>
<td>0.701</td>
<td>0.00586</td>
<td>0.015231</td>
<td>-0.02437 to 0.036086</td>
<td></td>
</tr>
<tr>
<td>15CPD 90 DAYS</td>
<td>0.546</td>
<td>98</td>
<td>0.586</td>
<td>0.01006</td>
<td>0.018419</td>
<td>-0.02649 to 0.046612</td>
<td></td>
</tr>
</tbody>
</table>
COMPARISON OF MONOCULAR DEFOCUS CURVE
Gr-1(ICB00) Vs Gr-2(ZCB00)

<table>
<thead>
<tr>
<th>POWER</th>
<th>1.00 D</th>
<th>0.5 D</th>
<th>0.0 D</th>
<th>-0.50 D</th>
<th>-1.00 D</th>
<th>-1.50 D</th>
<th>-2.00 D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ICB00</strong>&lt;br&gt;Gr-1(Mean)</td>
<td>0.22</td>
<td>0.12</td>
<td>0.05</td>
<td>0.07</td>
<td>0.10</td>
<td>0.25</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>ZCB00</strong>&lt;br&gt;Gr-2(Mean)</td>
<td>0.25</td>
<td>0.19</td>
<td>0.09</td>
<td>0.09</td>
<td>0.19</td>
<td>0.50</td>
<td>0.45</td>
</tr>
<tr>
<td>Mean difference</td>
<td>-0.07</td>
<td>-0.07</td>
<td>-0.04</td>
<td>-0.02</td>
<td>-0.086</td>
<td>-0.2523</td>
<td>-0.0989</td>
</tr>
<tr>
<td>P Value</td>
<td>0.003</td>
<td>0.000</td>
<td>0.001</td>
<td>0.000</td>
<td><strong>0.000</strong></td>
<td><strong>0.000</strong></td>
<td><strong>0.000</strong></td>
</tr>
<tr>
<td>Standard error of difference</td>
<td>0.00888</td>
<td>0.01779</td>
<td>0.01255</td>
<td>0.00342</td>
<td>0.0214</td>
<td>0.0219</td>
<td>0.0073</td>
</tr>
<tr>
<td>&lt; 95% CI of difference</td>
<td>-0.04432</td>
<td>-0.09967</td>
<td>-0.06676</td>
<td>-0.0316</td>
<td>-0.1278</td>
<td>-0.2956</td>
<td>-0.1132</td>
</tr>
<tr>
<td>&gt; 95% CI of difference</td>
<td>-0.00928</td>
<td>-0.02949</td>
<td>0.01724</td>
<td>0.0183</td>
<td>0.0434</td>
<td>0.2089</td>
<td>0.08435</td>
</tr>
</tbody>
</table>
Monocular Defocus Curve is significantly better in Gr-1 at -1.00D, -1.50D & -2.00D

**MONOCULAR DEFOCUS CURVE**

The Graph line chart for mono-ocular defocus curve showed Gr-1 (ICB00) has significantly better vision at vergence of -1.00 D, -1.50 D, -2.00 D (P < 0.05) and non-significant at -2.5 D (P = 0.053)

**SPECTACLE INDEPENDENCE FOR INTERMEDIATE DISTANCE (60cm)**

<table>
<thead>
<tr>
<th></th>
<th>ICB00 (Gr-1)</th>
<th>ZCB00 (Gr-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SPECTACLES REQUIRED</strong></td>
<td>10% (n=5)</td>
<td>86% (n=43)</td>
</tr>
<tr>
<td><strong>SPECTACLES NOT REQUIRED</strong></td>
<td>90% (n=45)</td>
<td>14% (n=7)</td>
</tr>
</tbody>
</table>

Spectacle independence was more in Gr-1 than Gr-2 for intermediate distance at 60cm. The difference is statistically significant. (p = 0.000) (Cross tab ChiSquare test)
Spectacles Independence Score for intermediate activities significantly better in Gr-1 (proportion satisfied ~100%, P value = 0.000)
Both the groups had comparable satisfaction for night time activities and comparable halos and glare during night driving (p > 0.05).

DISCUSSION

- Earlier there were insufficient reports to compare our study results.
- With the recently published studies our study shows comparable results, for better uncorrected intermediate distance visual acuities, broader defocus curve and more spectacle independence for intermediate distance activities for Gr-1(ICB00 IOL) vs Gr-2(ZCB00 IOL).\(^{1,2,3,4}\)
- Study by Auffarth et al showed similar comparable photic phenomenon and contrast functions in both IOLs which was similar to our study.\(^5\)
- Study by Vega et al shows lower MTF scores in ICB00 IOL at pupil sizes < 2 mm but comparable MTF scores in pupil sizes > 3.5 mm. However in our study Gr-1 (ICBO0 IOL) and Gr-2 (ZCBOO IOL) MTF values were comparable.\(^6\)

CONCLUSION

- Implantation of non-diffractive extended vision IOL provided
  - Extended range vision
  - Low incidence of unwanted photic phenomena
- Enhance ICB00 IOLs give spectacle independence for intermediate distance with good visual acuity for distance while maintaining the optical quality.

REFERENCES

1. Mencucci, Rita MD; Cennamo, Michela MD; Venturi, Daniel MD; Vignapiano, Roberto MD; Favuzza, Eleonora MD Visual outcome, optical quality, and patient satisfaction with a new monofocal IOL, enhanced for intermediate vision: preliminary results, Journal of Cataract and Refractive Surgery: March 2020 - Volume 46 - Issue 3 - p 378-387 doi: 10.1097/j.jcrs.0000000000000061


873–880. doi:10.1016/j.jcrs.2013.01.031


Multifocal Intraocular Lens Implantation In Pediatric Eyes

Dr. Minnu Parakal

INTRODUCTION

Paediatric cataract accounts for 7.4% – 15.3% of childhood blindness\(^1\) and a significant amount of avertable disability-adjusted life years. There is no gender or laterality based difference in the prevalence.\(^2\) India has a burden of around 280,000–320,000 visually impaired children.\(^3\)

Preoperative factors play an important role in the postoperative outcomes in children. The age of onset, type of cataract, laterality, delay in presentation, best-corrected distance visual acuity at presentation, the presence of strabismus, nystagmus, and glaucoma are all predictors of postoperative visual outcomes.\(^4\) The delay in presentation for surgery is associated with poor outcomes. Bilateral cataract has better visual outcome compared to unilateral cataract, 78% of the children with bilateral cataract had more than 0.3 visual acuity.\(^4\)

Age at which an Intra-ocular lens (IOL) can be implanted is a controversial issue. Implantation of an IOL in very young children carries the risk of severe postoperative inflammation, posterior capsule opacification and secondary glaucoma that may require
more surgeries. Accuracy of the IOL power calculation is affected by the small size of eyes and the steep keratometric values at this age. Furthermore, choosing an appropriate IOL power is not a straightforward decision as future growth of the eye may result in an unexpected refractive error as children age. There are very few studies that have documented the implantation and subsequent results of multifocal IOL’s.

AIM OF THE STUDY

The study aims at understanding the merits and demerits of implanting a Multifocal IOL after cataract extraction in the pediatric group. This study analyses the visual outcome after surgery, the behaviour of lens inside the eye, the reaction of eye after surgery and the possible intra-operative and post-operative complications. It also assess the visual performance of the child in scotopic and photopic conditions, in day to day life.

METHODS

This was a prospective interventional study done in a tertiary hospital in Kerala during the time period from August 2017 to December 2019. 21 eyes of 14 children who developed cataract were included in the study. They were in the age group of 1 year to 14 years. The ethical standards as outlined by the Medical Research Council were followed when contacting patients. A well informed consent was taken from the patients’ parents and the study protocol was approved by the ethics committee. The age of the patient, cause for cataract, laterality, preoperative and postoperative uncorrected and corrected distance and near visual acuity, axial length, slit lamp observations, preoperative and postoperative intraocular pressures, age of surgery, type of surgery, postoperative IOL positioning, intra and post operative complications and quality of life estimation were recorded. All patients were followed up for a minimum of 3 months post surgery. All children were advised to undergo part time occlusion of the normal eye in case of unilateral cataracts and alternate eyes in case of bilateral cataracts, the time period of which was determined based on resistance to occlusion in preverbal children and on visual acuity in older ones.
Visual acuity was assessed by Snellen’s chart in older children, LEA symbol chart in pre-school children, Bock’s candy bead test, Langs stereopsis chart and fixation quality and preference (CSM) in preverbal children. Contrast sensitivity was assessed by Pelli Robson contrast sensitivity chart in older children.

In younger children, ultrasound biometry under ketamine sedation was done and SRK II formula was used for IOL power calculation. In older children, optical biometry was done as an OP procedure and Barrett’s universal formula was used. Children of 5yrs and more were implanted the same IOL power as calculated. In children less than 5yrs of age, eye was undercorrected by 10%. All underwent primary IOL implantation under general anaesthesia. Bilateral cataract patients underwent cataract extraction in both eyes simultaneously with IOL implantation.

**STEPS OF THE SURGERY:**

Under sterile precautions, superior 3 mm scleral incision and sclerocorneal tunnel was made. Paracenteses were made at 9.30 o’clock and 2.30 o’clock position. After staining the anterior capsule with Trypan blue, anterior continuous curvilinear capsulorhexis was done with a rhexis forceps, the pull directed centrally. Lens was aspirated with an irrigation-aspiration handpiece. Posterior continuous curvilinear capsulorhexis (PCCC) along with anterior vitrectomy were done. A single piece hydrophobic yellow chromophore containing acrylic multifocal IOL was inserted into the capsular bag. Remaining visco-elastic substance in AC was washed off and the corneal incisions were sutured after a peripheral iridectomy.

Posterior continuous curvilinear capsulorhexis and anterior vitrectomy was done in all except 4 eyes. The multifocal IOL used were MF Restor with add of +3 D, and Tecnis MF with add of +4 D for near vision correction.
Post operative IOL positioning was evaluated with respect to the number of rings exposed on either side of the IOL centre in the pupillary area. Presence of IOL glistening on slit lamp examination was noted. Slit lamp examination was done using either the handheld or standard slitlamp microscope.

For assessing the quality of life after cataract surgery, a questionnaire was prepared and it was modified Cardiff Visual Ability Questionnaire for Children. (chart 1)

SPSS ver21 was used for data analysis and the outcomes were documented.

<table>
<thead>
<tr>
<th>MODIFIED CARDIFF VISUAL ABILITY QUESTIONNAIRE FOR CHILDREN (CVAQC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAME</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>GRADE</td>
</tr>
<tr>
<td>EXCELLENT</td>
</tr>
<tr>
<td>FAIR</td>
</tr>
<tr>
<td>POOR</td>
</tr>
</tbody>
</table>

1. reading textbooks and work sheets?
2. reading the smallest print in the book?
3. drawing, colouring or painting?
4. reading text messages on your mobile phone?
5. watching television?
6. watching a film at the cinema?
7. going out alone in the daylight?
8. walking inside home at low lit condition?
9. walking in a crowded place?
10. reading bus/train time table on a screen at a station?
11. recognizing faces or identifying relatives at arms length?
12. recognizing faces or identifying relatives from a distance?
13. playing video games or mobile?
14. Playing inside home?
15. playing outside home?
16. pick up small object from floor?
17. following movements of mother / attending person?


RESULTS

21 eyes of 14 pediatric patients in the age group of 1 to 14 years were included in this study, out of which 7 children underwent bilateral surgery. The average axial length was 22.53 mm, ranging between 20.2 mm and 26.87 mm with a standard deviation of 1.74.

The average age at which IOL implantation was done was 5.19 yrs, ranging from 1 to 14 years. All except 3 underwent primary IOL implantation. The average multifocal intraocular
lens (MFIOL) power was 23.07 D +/- 4.09 D. The lowest MFIOL power implanted was 14.5 D in a 14 year old child.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>LogMar Mean</th>
<th>SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRE OP VN</td>
<td>21</td>
<td>0.8 (6/38)</td>
<td>0.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>POST OP VN</td>
<td>21</td>
<td>0.3 (6/12)</td>
<td>0.34</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Comparison of pre operative and post operative distant vision

p-value < 0.05, there is significant improvement in distant vision. (preop vn - preoperative vision)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>LogMar Mean</th>
<th>SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREOP VN</td>
<td>15</td>
<td>0.5 (N10)</td>
<td>0.24</td>
<td>0.027</td>
</tr>
<tr>
<td>POST OP VN</td>
<td>15</td>
<td>0.3 (N6)</td>
<td>0.12</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Comparison of pre operative and post operative near vision

p-value < 0.05, there is significant improvement in near vision. (postop vn - post operative vision)

The logmar best corrected visual acuity for distance and near (courtesy: David B, Elliott and John G Flanagan. Assessment of visual function. Ophthalmology, published on 08/03/2015) improved in 100 % of eyes. The average corrected distant visual acuity was 0.3 (6/12) and average near vision was 0.3 (N6) without near addition. 66.7 % cases had post surgery uncorrected distant vision of 6/12 or better and 73.3 % had uncorrected near vision of N8 or better. The average residual spherical power was 0.26DS and astigmatism was -0.22DC.
The age at which IOL implantation was done and the percentage of improvement of vision in each eye were studied and the correlation between the two was analysed. There was no correlation noted between the two in our study.

<table>
<thead>
<tr>
<th>Age of surgery</th>
<th>Change in Distance vn</th>
<th>change in near vn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Correlation</td>
<td>0.147</td>
<td>-0.404</td>
</tr>
<tr>
<td>p-value</td>
<td>0.525</td>
<td>0.217</td>
</tr>
<tr>
<td>n</td>
<td>21</td>
<td>15</td>
</tr>
</tbody>
</table>

Table 3: correlation of age of surgery with vision improvement

No correlation with age and vision improvement.

The average contrast sensitivity in verbal children post surgery was 1.5. Stereopsis was attained in all verbal children (600 - 40sec of arc).

No intra-operative complications occurred in any of the cases. No IOL decentration was noted in any of the cases at follow up visits. There was transient rise in intraocular pressure (IOP) in 9 eyes immediate post surgery, but became normal within 1 month. The average IOP at 1 month was 13.71 mm Hg. Three patients developed visual axis opacification and underwent Nd: YAG capsulotomy at an average of 5 months post surgery.

The quality of life questionnaire indicated satisfactory levels of performance at school and play, and in both photopic and scotopic light conditions. There was no indication of intolerance to light or poorer performances in low light situations.

DISCUSSION

The visual prognosis for children with congenital cataracts has improved dramatically since it was first recognised that cataract surgery during infancy is critical for a good visual outcome;[5,6] however, the optimal time to perform the surgery is still in question. Anecdotal reports have noted excellent visual outcomes in neonates undergoing cataract
surgery during the first week of life \cite{5,7}; however, a subsequent analysis of 45 children with dense unilateral cataracts, who underwent cataract surgery, found that the visual outcome was the same regardless of when the surgery was performed during the first 6 weeks of life. \cite{8} While the same analysis has not been performed on children with bilateral congenital cataracts, it has been proposed that the critical period for treating children with bilateral congenital cataracts may extend to 8 weeks of life. \cite{6,9,10} Paediatric ophthalmologists are now trying to determine the optimal time to perform cataract surgery to reduce the high incidence of complications that have been reported following cataract surgery during infancy. Owing to the giant leap in cataract surgery technology and technique of pediatric cataract surgery, the post surgery complications are now few.

According to Infant Aphakia Treatment Study (IATS), there was no significant difference in visual acuity at age one year between those who underwent primary IOL implantation and those who were left aphakic and given contact lens correction, though the IATS found a higher number of surgeries in children who had IOLs at < 1 year. \cite{11} Despite controversy, IOLs are implanted in infants with increasing frequency. Some have advocated surgery based on age as follows: 1. Infants less than 6 months to undergo lens aspiration, primary posterior capsulectomy and anterior vitrectomy. IOL implantation in children less than 6 months is still controversial. \cite{13} 2. Primary IOL implantation is to be the standard of care in patients over two years of age. There is increasing evidence of safety in those less than 2 years. \cite{14} A survey by the American Association for Pediatric Ophthalmology and Strabismus reported an increase in IOL implantation in children less than 2 years from 12.9% to 81.9% from 1993 to 2001. Some have advocated implanting IOLs at an even younger age less than 6 months in cases of unilateral cataract with no contraindications such as microphthalmia or structural abnormality. \cite{15} Ledoux et al. reported a 14 year retrospective review of 239 children (aged 11 days to 17 years), with unilateral and bilateral cataracts who underwent primary IOL implantation. \cite{16} They found approximately 75% achieved 0.3 vision or better and with better outcomes in bilateral
cases and in children who were older than 1 year prior to IOL implantation.\textsuperscript{[16]} In a retrospective study of 400 patients with 87\% of the cohort undergoing primary IOL implantation, Congdon et al. reported that 40\% achieved 20/60 vision or better.\textsuperscript{[17]} Congdon et al. concluded that IOL implantation with spectacle correction predicted a better visual outcome.\textsuperscript{[17]} A study of primary IOL implantation in 120 eyes of 80 children below 2 years of age concluded that IOLs were safe and can be considered as a viable option for visual rehabilitation.\textsuperscript{[17]} We have found that all children increased their visual acuity from an average of 0.8 to 0.3, including very young and old children. The youngest children to be implanted in our study was 1 yr old, as we follow a protocol of aphakia and contact lens post cataract surgery below 1 year of age. The oldest child was 14 year old and though she underwent surgery beyond the age of plasticity, her vision did improve substantially from 1 to 0.6. This could be because of a progressive developmental cataract rather than a stationery congenital cataract that may be less amblyogenic.

Multifocal IOLs provide good near and distance vision\textsuperscript{[18]} and also help in establishing stereopsis in unilateral cases,\textsuperscript{[19]} but the brightness and contrast of the images get compromised.\textsuperscript{[18]} Any decenteration of lens leads to glare, halos, and deterioration in the quality of the image. The spectacle independence should not be expected with multifocal IOLs in children, but the multifocal IOL provides independence from bifocals and will still be able to provide distance vision correction with refractive surgery in the patients’ adult future. Also, as near vision is more important to ward off refractory amblyopia, IOLs which provide good near vision also are likely to be a better option.

Jacobi et al.\textsuperscript{[12]} report on their experience implanting multifocal IOLs in 35 eyes of 26 pediatric patients aged 2 to 14 years. They suggest that for children, multifocal IOLs are a viable alternative to the standard monofocal IOL. However, this study has limitations. The reported benefit of improved stereopsis may come from improved acuity. Data on spectacle dependence and subjective satisfaction are not helpful when obtained from
children, who will understate their symptoms in the hope of avoiding glasses. The average follow-up of 27 months (range, 12 – 58 months) is good for adults but is not sufficient for pediatric patients.

In our patients, the parents were given a choice of monofocals and multifocals, with the advantage of multifocals being added near visual acuity. They were counselled about additional distance and near glasses also, though most children required correction for astigmatism and none required near augmentation. This itself may show that correcting near vision in the IOL may be a more physiological means for children than giving bifocals.

Lee ES et al [20] studied the visual acuity (VA) and patient satisfaction after implantation of Array SA40N multifocal intraocular lens (IOL) (AMO) in adult polulation. Three months postoperatively, uncorrected distant and near vision, uncorrected distant vision under glare conditions, and contrast sensitivity were good in all eyes and more than 72% of patients never wore glasses for near vision.

In our study, the good reference with respect to contrast assessment is an indication of the tremendous adaptability of children’s eyes to light distribution by the IOL and resultant aberration like glare, as even the older children failed to report it when questioned directly.

3 of 21 eyes (14%) developed visual axis opacification though they had already undergone posterior capsulorhexis (PCCC). This could be because of inadequate anterior vitrectomy that would have provided a scaffold for lenticular tissue to proliferate.

IOP rose only transiently in 9 eyes immediate post surgery. This could have been because of retained OVD’s, steroid response or an immediate inflammatory response. None of the children had a primary glaucoma and we were able to achieve normal IOPs after a brief period of treatment of transient glaucoma.
The inadequacy of the study include, 1. Short period of follow up being 3 months for some eyes, 2. Small sample size, 3. Difficulty in extracting qualitative information from children in terms of abstract phenomena like dysphotopsia and glare associated with diffractive multifocals is also an impediment.

CONCLUSION

For children, near vision is more important than distant vision, as they need clear near vision for their daily activities like playing, drawing, etc. Smaller children may not be compliant with spectacle or contact lens use, especially when having working parents. Also children with bifocals may not use the spectacle segments properly. All these are causes for amblyopia.

Multifocal IOL implantation is a better alternative to monofocal IOL for paediatric cataract as the patient has good near vision postoperatively, without using a bifocal glasses. This prevents development of amblyopia in such patients. The post operative complication rate associated with IOL was virtually nil in our study and a high degree of visual improvement was obtained.

REFERENCES


Comparison Of Clinical Outcomes Between Image-Guided System Versus Smartphone Digital Reference Marker App for Toric Intraocular Lens Implantation In Cataract Surgery

Dr. Swati Agarwal, Dr. Ajoy Paul, Dr. Sagar Bhargava

ABSTRACT

PURPOSE:

To compare the clinical outcomes between Verion Image - Guided System versus a Smartphone digital reference marker app for toric intraocular lens (IOL) implantation in cataract surgery.

SETTING:

Tertiary Eyecare Centre, India

DESIGN:

Prospective randomized clinical study.
METHODS:
Eyes with regular corneal astigmatism of more than 1.5 dioptres (D) that required cataract surgery and toric IOL implantation (Acrysof SN6AT3-T9) were randomly assigned to the image-guided group or the smartphone app digital reference marker group. Postoperative outcome was measured by uncorrected distance visual acuity (UCDVA), residual astigmatism and deviation from the target anticipated residual astigmatism.

RESULTS:
The study enrolled 23 eyes (20 patients). The postoperative UCDVA of all the eyes in both the groups were Snellens 6/9; LogMAR 0.18 and better. The mean postoperative UCDVA for the image marking group was 0.14 ± 0.066 logarithm of minimum angle of resolution (LogMAR) and for the smartphone toric marking app group was 0.138 ± 0.058 LogMAR (t test 0.942). The mean residual refractive cylinder was 0.154 ± 0.184 D and 0.175 ± 0.195 D in the image-guided group and smartphone toric marking app group, respectively (t test 0.804). The mean of the deviation between target anticipated residual astigmatism and actual residual astigmatism in the image guided group was 0.197 ± 0.158 D versus 0.157 ± 0.129 D in the smartphone toric marking app group (t test 0.532).

CONCLUSION:
There was no significant difference in UCDVA, residual refractive astigmatism or deviation from target anticipated residual astigmatism between the image guided digital marking system versus smartphone digital reference marker app in Toric IOL cataract surgery.

It has been estimated that 30 % of patients with cataract have more than 0.75 D of corneal astigmatism, that 22 % have more than 1.50 D, and that 8 % have more than 2.00 D of corneal astigmatism [1-2]. Toric IOLs are an indispensable tool for optimising refractive outcomes, visual performance and patient satisfaction after cataract surgery [3,4]. Toric
IOLs provide better postoperative UCVA, greater spectacle independence, and lower postoperative astigmatism compared to non-toric and non-toric IOLs + relaxing incision.

Today’s cataract patients expect optimal vision after intraocular lens implantation, and those who choose toric IOLs do not expect to have to wear glasses or contact lenses full time after cataract surgery. The accuracy of the toric IOL surgery depends on the following factors: Appropriate patient selection, accuracy of the biometry and keratometry, accuracy of the calculator being used, accuracy of the preoperative reference markings, accuracy of the IOL placement in the capsular bag and rotational stability of the IOL.

Prediction of astigmatic outcomes with toric IOLs can be improved with appropriate measuring devices and methods to establish the required toric IOL power. Keratometric readings can be obtained by different devices like automatic and manual keratometry, Topographer, Verion, etc. In case of discrepancy between values an integrated K reading can be generated using vector analysis in the current Barrett’s toric calculator. The integrated K is significantly more accurate than a value from a single device and thus significantly eliminates any keratometric errors. The Barrett toric calculator had the lowest mean absolute error in predicted residual astigmatism (0.35 to 0.54 D, all devices) compared with the Alcon and Holladay toric calculators with or without the Baylor nomogram (P < .021). The new Barrett calculator theoretically accounts for Posterior corneal astigmatism (PCA) in With the rule (WTR) and Against the rule (ATR) astigmatic eyes, axial length and anterior chamber depth in Effective lens position (ELP) estimates permitting more precise astigmatic prediction. Barrett online toric calculator is thus the most accurate online toric calculator available as of date.

IOL alignment is crucial to refractive success; for every degree of misalignment, there is a reduction of 3.3% of the astigmatism correction. The manual preoperative reference markings are done with patient sitting and head erect. These markings can be slit-lamp
assisted with pendulum or gravity marker, bubble marker, free hand, or with smartphone digital reference marker app [13-15].

Smartphone assisted digital reference marking is a simple, inexpensive, and precise method to measure the toric IOL axis using a camera-enabled and gyroscope assisted cellular phone [16]. Applications like the “iToric Patwardhan” on the android platform (Dr S. Patwardhan) and the ‘toriCAM’ [17] on the iOS platform (Dr. G. Barrett – iOS), are available free of cost and can determine the exact axis of the corneal limbal marks as a reference to find the correct alignment for a toric IOL during surgery. Alternatively natural landmarks of the conjunctiva can be used instead of applying ink marks on the limbus to get a digital reference. Mark-less IOL alignment can be achieved by image-guided systems like VERION image-guided system (Alcon, Fort Worth, Texas), CALLISTO Eye and Z align (Carl Zeiss Meditec, Jena, Germany), and TrueVision 3D Surgical system, Santa Barbara, California). Image guided systems also aid in planning the incisions, capsulorhexis size, and optimal IOL centration. VERION Digital Marker (VDM) uses multiple reference points on the conjunctiva and limbus such as scleral vessels, limbal vessels and iris features to create a digital overlay between the live surgery image and image taken preoperatively. It then projects the desired implantation axis of the toric IOL into the right ocular of the surgeon’s microscope while using eye tracking navigation to account for cyclotorsion and eye movement. Thus, VERION Image guided system claims to ‘minimise data transcription errors, improvement in clinical efficiency, toric and multifocal IOL confidence, ensures surgical consistency, and optimises visual outcomes’ [18].

VERION™ guidance delivers better outcomes than slit-lamp assisted and conventional manual ink-marking techniques in terms of induced astigmatism [19-22]

In this study, we intend to compare between the VERION image-guided system and the iToric Smartphone digital reference marker app, clinical outcomes with respect to uncorrected distance visual acuity (UCDVA), residual astigmatism and deviation from
target residual astigmatism in a toric IOL cataract surgery. To our knowledge there has been no previous published studies or reports of this.

METHOD

This is a prospective randomised clinical study conducted at a tertiary eyecare centre. The study included 23 eyes of 20 patients undergoing phacoemulsification cataract surgery with coexisting corneal astigmatism more than 1.5 dioptre (D). The eyes were randomly assigned to either digital image guidance using VERION digital marker or Smartphone app assisted digital reference marking. Sample size for smartphone digital reference marking app group was 10 (n = 10) and for the VERION image guided digital marking system group was 13 (n = 13).

Detailed slit-lamp evaluation was done for every patient and those with corneal or retinal pathologies, irregular astigmatism, high axial length, history of previous ocular or intraocular surgery, ocular trauma and amblyopia were not included in the study.

A compromised ocular surface may skew keratometric measurements by up to 2.5 D [23]. Topography has been done for every patient to evaluate and rule out patients with irregularities on the ocular surface. Irregular topography can indicate corneal disease, such as severe dry-eye disease, ocular surface disease, basement membrane dystrophy or some other subtle corneal pathology that may have been missed. Diffuse irregularity on topography is often consistent with dry-eye disease, and this can be confirmed using vital dye staining and examining tear breakup time at the slit lamp. One of these conditions could be inducing the astigmatism.

OCT was preoperatively done for every patient to rule out any apparent or obvious retinal pathology.

Keratometry was performed on multiple devices viz auto and manual keratometer, topographer for smartphone assisted making group. Keratometric analysis on VERION was done in addition for the VERION image guided IOL implantation group. Integrated K
reading was taken in calculation whenever there was a discrepancy in K readings between the devices. Biometry was performed by Immersion method in all the cases. Toric IOL power and axis of implantation was decided by Barrett online toric calculator.

For the smartphone app digital reference marker group, with the patient seated on operation table, an arbitrary point was marked at the limbus. The point was sharp and did not smudge. A flashlight was shone at glabella and patient focussed straight on a distant point. Using the gyroscope assisted camera of iToric app a snap was taken. Image was zoomed to fit the outer circle at limbus. Using the protractor, the red line was dragged to pass through the centre of cornea and the red dots were placed on the marks at limbus to get the axis of marks [Fig.1]. By taking into account the gyroscopic assisted camera rotation, we get the effective mark rotation from the 0 - 180 axis. Thereafter on operation table after sterile draping, Mendez ring was aligned at 0 - 180 degree by keeping the mark at effective rotation axis.

Figure 1: Finding the exact axis of marks with the iToric app by dragging the red line through centre of cornea and on the marks.
For the VERION Image guided group, after planning of the surgical procedure in VERION reference unit, data was exported to VERION digital marker (VDM) located in the operating room. This allows the surgeon to see in one of the oculars of the operating microscope in real-time a digital tracking overlay picture after the intraoperative image registration. This system automatically corrects the cyclotorsion by recognising scleral vessels and landmarks of the iris and visually guides the surgeon for the size and location of corneal incisions and capsulorhexis [fig 2]. It shows the axis of IOL implantation and also assists the surgeon in controlling the IOL centration.

![Figure 2: VERION overlay showing the location of corneal incisions](image)

Figure 2: VERION overlay showing the location of corneal incisions
To reduce any IOL related confounding factors like rotational stability, Acrysof IQ Toric platform (SN6AT3-T9) was used in all cases [24]. Surgeries were performed by a single surgeon to reduce any surgeon related variables like surgically induced astigmatism (SIA), effective lens position (ELP), IOL alignment techniques, etc. Surgeries were done with 2.8 mm main incision at 90 degrees. No intraoperative complication was encountered in any of the cases. In postoperative period, IOL alignment was checked on slit lamp at 1 hour. At postoperative 14 days, patient was evaluated for IOL rotation. However, no rotation was encountered in our study.

Residual astigmatism decreases the postoperative visual outcome with respect to optical clarity, contrast sensitivity and overall patient satisfaction [25]. In this study we use UCDVA, BCDVA, Residual astigmatism, deviation from target residual astigmatism as a measure of the clinical outcome of toric IOL surgery.
Data was entered in Microsoft Excel. Using the software, mean and standard deviation was calculated for the different samples and unequal Variance (Independent) unpaired t-test was done to analyse for any significant difference between the two groups.

RESULTS

23 eyes of 20 patients were used for data analysis of which the sample size smartphone digital reference marking app group was 10 and for the VERION image guided digital marking system group was 13. Unequal variance unpaired t test was used to analyse. Results of the analysis are shown in table1. The postoperative UCDVA of all the eyes in both the groups were Snellens 6/9; LogMAR 0.18 and better.

The mean postoperative UCDVA for the image marking group was 0.14 ± 0.066 logarithm of minimum angle of resolution (LogMAR) and for the smartphone toric marking app group was 0.138 ± 0.058 LogMAR (t test 0.942).

The mean postoperative BCDVA for the image guided digital marking group was 0.10 ± 0.065 LogMAR and for the smartphone digital reference marking app group was 0.074 ± 0.079 LogMAR (t test 0.407).

The mean residual refractive cylinder was 0.154 ± 0.184 D and 0.175 ± 0.195 D in the image-guided group and smartphone toric marking app group, respectively (t test 0.804).

The mean of the deviation between target anticipated residual astigmatism and actual residual astigmatism in the image guided group was 0.197 ± 0.158 D versus 0.157 ± 0.129 D in the smartphone toric marking app group (t test 0.532)
DISCUSSION

Our results demonstrated that there is no significant difference between the uncorrected refractive error, residual astigmatism, or deviation from target residual astigmatism in both the image guided digital marking group and the smartphone digital reference marker app group.

This demonstrates that using VERION image guided digital marking system over smartphone digital reference marking app did not lead to significant improvement with respect to clinical outcomes.

It should be noted that there are some important differences between the present study and the previously conducted studies. The earlier studies demonstrated a strong agreement between the between the VERION and smartphone axis marking but assumed VERION image guided system as the gold standard for accurate alignment of the toric IOLs

<table>
<thead>
<tr>
<th></th>
<th>Smartphone digital reference marking app group</th>
<th>VERION image guided digital marking group</th>
<th>t test</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCDVA</td>
<td>0.138 ± 0.058 LogMAR</td>
<td>0.14 ± 0.066 LogMAR</td>
<td>0.942</td>
</tr>
<tr>
<td>BCDVA</td>
<td>0.074 ± 0.079 LogMAR</td>
<td>0.10 ± 0.065 LogMAR</td>
<td>0.407</td>
</tr>
<tr>
<td>Residual astigmatism</td>
<td>0.175 ± 0.195 D</td>
<td>0.154 ± 0.184 D</td>
<td>0.804</td>
</tr>
<tr>
<td>Deviation of residual astigmatism from target anticipated astigmatism</td>
<td>0.157 ± 0.129 D</td>
<td>0.197 ± 0.158 D</td>
<td>0.052</td>
</tr>
</tbody>
</table>

Table1: Comparison between Smartphone digital reference marking and VERION image guided digital marking
considerable advantage in the design of the current study is the ability to independently evaluate and compare the clinical outcomes of the two marking systems.

Smartphone digital reference marker apps are a cheap consistent and reproducible way of enhancing outcomes of Toric IOLs. Ophthalmic toric marking apps are easily available and can turn smartphones into sophisticated medical devices. It should be noted that smartphone assisted digital reference marking needs a lot of care, precision and is prone to transcription errors.

VERION image guided system aims to make the process of toric IOL alignment more accurate and potentially offers a way to limit sources of error. It enhances the surgical flow especially in a high-volume centre and reduces the surgical time. Sometimes intraoperative registration may not be successful if the patient is uncooperative or anxious or there is a development of conjunctival chemosis. Also due to its high cost, it may not be an economically viable option for majority of ophthalmologists. There is no doubt that the estimation of the ability of any device to provide repeatable, reproducible and reliable outcomes is equally significant as the evaluation of its other characteristics. The measurements performed with the SensoMotoric instrument (SMI) Reference Unit showed an acceptable intrasession repeatability for astigmatism magnitude, but a moderate repeatability for the meridians of astigmatism[27]. So, an evaluation of intra-observer and inter-observer variability of VERION reference system should be done in future.

The limitation of this study is that it provides results obtained by a single surgeon. Though this helps eliminate surgeon variables like surgically induced astigmatism, ELP, surgeon related alignment accuracy; a multivariate evaluation should be performed in the future to evaluate the clinical accuracy of the two systems in different hands.
CONCLUSION

There was no significant difference in UCDVA, residual refractive astigmatism or deviation from target anticipated residual astigmatism between the image guided digital marking system versus smartphone digital reference marker app in Toric IOL cataract surgery.

ACKNOWLEDGEMENTS

The ‘iToric Patwardhan’ mentioned in the study is a free app available on android smartphones and developed by Dr Sourabh Dileep Patwardhan. The authors have no financial or propriety interests in it.

CONFLICT OF INTEREST STATEMENT

The authors have no funding and conflicts of interest to disclose.

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Sewing Needle Micro Capsulotomy : New Technique To Prevent Argentinian Flag Sign

Dr. Rajendra Prasad, Dr. Anurag Badhani, Dr. Geetika Dogra, Dr. Arvind Morya

ABSTRACT

The Argentinian flag sign is a known complication in intumescent white cataracts, which arises instantly after an initial prick with a sharp hypodermic needle on a stretched out anterior capsule. Increased intralenticular pressure is believed to be responsible for propagation of the initial prick into a radial capsular tear. However, it is the 'linear cut' configuration of the initial prick, created by the hypodermic needle on the tense anterior capsule, which spontaneously opens up and propagates towards the periphery along its margins. To overcome this we devised a novel instrument sewing needle microcapsulotome to puncture the capsule and create a single or multiple round openings with smooth margins allowing the bag to decompress satisfactorily without yielding to disruptive intralenticular forces. This technique of sewing needle microcapsulotomy, to prevent Argentinian flag sign, was found to be highly effective and safe in a series of surgeries on intumescent cataracts.
INTRODUCTION

Intumescent white cataracts pose various challenges for the operating surgeon. These forms of cataracts have liquified, hyper-hydrated and swollen lenticular material, with increased intralenticular pressure and a relatively tense stretched out anterior lens capsule. Once the surgeon attempts to begin the capsulorhexis, a spontaneous radial extension of the capsular tear towards the periphery may occur. The Argentinian Flag Sign, a well known complication during capsulorhexis in intumescent white cataracts, is the appearance of the stained blue anterior capsule on either sides of the white cataract, mimicking the pattern of Argentina’s flag, and was described by Daniel Mario Perrone, MD. [1]

In some cases this radial extension of the tear may occur later during the course of continuous curvilinear capsulorhexis due to various other factors. These include insufficient chamber maintenance with viscoelastic devices or excess posterior pressure such as exhibited during patient exertion or valsalva. [2] The loss of rhexis margin may even extend to the posterior capsule leading to vitreous loss, loss of lens material to the posterior segment, poor capsular support for intraocular lens implantation as well as corneal endothelial damage from extensive intraocular manipulation and extended surgical time. [3,4,5,6] This adversely affects the anatomical and functional results of surgery.

It is therefore prudent to prevent Argentinian flag sign formation in intumescent white cataracts. Several methods have been described such as Femtosecond laser assisted capsulotomy, Nano-pulse capsulotomy (Zepto, Mynosys Cellular Devices, Inc.) and Capsulaser (Excel-Lens, Inc.), which employs selective absorption of the laser by the trypan blue stained capsule to create a capsulorhexis. Although these technologies automate the capsulotomy and reduce the dependence on surgical skill, they also add significantly to the cost of the cataract procedure. [7] Phaco-capsulotomy is another technique where simultaneous puncture of the anterior capsule and decompression of the capsularbag is done with the help of phaco-probe [8] Potential complications of phaco-capsulotomy include wound burn and zonular dehiscence due to excessive manipulation. The configuration of capsular opening created is almost unpredictable.
and also has irregular margins, which may later aid in propagating a radial extension. \[^9\]

Furthermore, the safety and efficiency of these techniques to automate a complete capsulorhexis in intumescent cataracts have not been established yet.

Manual capsulorhexis techniques like two staged capsulorhexis or a mini-capsulorhexis have been described in intumescent cataracts to avoid Argentinian flag sign. \[^10,11\]\ Small needle aspiration technique is one such manual capsulorhexis technique, which has been used widely by many surgeons. \[^12,13\]\ This involves pricking the anterior capsule with a sharp 26 G or 30 G hypodermic needle followed by simultaneous aspiration of liquified lens matter to decompress the bag. A modified version of the same has been described wherein the capsular prick and aspiration is performed before creating the corneal incisions. In spite of using these techniques, peripheral extension of the capsular tear has still been frequently seen, during the hypodermic needle prick of the tense anterior capsule, even before initiating the aspiration of liquid cortex.

Despite many techniques the problem of radial extension of the capsular tear continues to be a challenge in intumescent white cataract surgery. Several mechanisms have been described earlier for the propagation of radial tear in these intumescent white cataracts. The concept of anterior and posterior pressurised intralenticular compartment system was put forth by, Figueiredo et al. They postulated that it is the posterior intralenticular pressure between the nucleus and posterior capsule of the lens, rather than the vitreous pressure, which pushes the nucleus forward and can lead to capsulorhexis extension even after the use of preoperative mannitol or aspiration of intralenticular fluid from the anterior compartment. \[^14\]

There had to be other factors responsible, which assist the raised intralenticular pressure to propagate the splitting of capsule after the initial prick, as it was noticed that the capsule usually splits open even before, or at times during the aspiration of liquified lens matter with sharp needle. We referred back to a series of surgical videos of intumescent white cataracts where Argentinian flag sign was noted. On close examination we noticed that the sharp beveled hypodermic needle (26 G, 30 G) being used to open up the anterior capsule to initiate rhexis and decompress the intralenticular pressure, always created a ‘linear cut’ along the plane of needle bevel. We also observed that the linear cut
configuration of the initial prick on a capsule under tension always extended radially and spontaneously along the open margins of the cut but never perpendicular to the linear cut. This configuration of the opening made on the capsule by the prick with a sharp hypodermic needle is what grabbed our attention.

In reality it is not only the raised intralenticular pressure which causes the extension of tear but it is the ‘linear cut’ configuration of the tear on the anterior capsule created by the sharp edge of the beveled hypodermic needle cystotome or sharp tipped rhexis forceps, responsible for the split in the anterior capsule. Raised intralenticular pressure with sudden forward thrust of the nucleus against the back of the anterior capsule triggers a disruptive force which thereafter splits the initial linear cut into a complete anterior capsular tear, spontaneously extending towards the periphery. This observation also adds to the known mechanism of occurrence of Argentinian flag sign in intumescent white cataracts. [Figure 1]

![FIGURE LEGENDS](image)

**FIGURE LEGENDS**

Figure 1: (A) Rajendra Prasad’s sewing needle microcapsulotome: Round pointed tip create round hole microcapsulotomy similar to mini capsulorhexis with round continuous circular edges without any discontinuity. (B) Ultra sharp beveled stain less steel
hypodermic needle: Sharp tip \textit{functions} like a knife and create a discontinuous slit when puncture the capsule.

Henceforth we came up with a hypothesis that if we were able to manually create an opening in the anterior capsule which had a round regular configuration, like a capsulotomy in true sense instead of a linear cut, we may provide resistance against the forward thrust of intralenticular pressure, thus preventing Argentinian flag sign. We incorporated the sewing needle tip to design to develop a novel instrument that would puncture the anterior capsule creating an opening which had a smooth round configuration, allowing liquified lens matter to egress and decompress the bag without propagating a radial extension of tear.

After a few rounds of modifications we came up with a unique but simple device, sewing needle microcapsulotome, a hook with a round knurled handle, angled 60 degree to the distal shaft which ends in a sharp pointed round tip approximately 0.75 mm in length, 0.60 mm in diameter, angled at 90 degree. [Figure 2, 3]

\section*{SURGICAL TECHNIQUE}

After routine incisions, the anterior capsule is stained with 0.06\% trypan blue dye to enhance the visibility \cite{9}. In accordance with soft shell technique, dispersive ophthalmic viscosurgical device (OVD) (Viscoat, DisCoVisc) is injected into the anterior part of the anterior chamber followed by flattening of the anterior lens capsule with the injection of highly cohesive OVD like sodium hyaluronate (1.4 \% Healon GV, 2.3 \% Healon 5).

Using the main corneal incision, sewing needle microcapsulotome is inserted into the anterior chamber and the tip of the needle is placed vertically at 90 degrees over the centre of the anterior capsule. Under direct visualisation, tip is then moved downwards to penetrate through the taut anterior capsule. Sewing needle microcapsulotome puncture creates a round opening with smooth margins at the centre of the anterior capsule. Once the process of microcapsulotomy is complete, the tip of microcapsulotome is removed vertically without making any sideways or horizontal movements [Figure 4,5].
On pricking the taut anterior capsule, pressurised intralenticular fluid spontaneously egresses out through the microcapsulotomy. Since the pointed round tip of microcapsulotome creates a round continuous hole, it provides resistance to the force of sudden outburst of intralenticular pressure, helping prevent the pre-evacuation splitting of anterior capsule.

As soon as the microcapsulotomy is successfully performed, complete decompression of the intralenticular compartment is further done by evacuation of the fluid with delicate shove, twist, and wobble manipulations of the nucleus with the visco cannula. Decompression of the posterior intralenticular compartment can be achieved by tipping the edge of the nucleus at equator posteriorly with the cannula tip so that the fluid trapped between nucleus and posterior capsule flows out anteriorly. More than one microcapsulotomies, around the central opening, can be created to release multiple pockets of fluid in the capsular bag. [Figure 5]

Once the decompression is complete, anterior chamber is reformed with cohesive viscoelastic to compensate for the loss of intralenticular volume and to pressurise the anterior chamber so that anterior capsule is flattened prior to initiation of the capsulorhexis. An intended 5.0–5.5 mm capsulorrhexis is initiated after tearing the central hole using a rhexis forceps and easily completed without the risk of peripheral extension of the rhexis.

Since nucleus in intumescent cataract is free within the liquefied cortico-epinuclear complex hydrodissection is generally not required. Nuclear segmentation is done with any suitable chopping technique and phacoemulsification is performed with standard parameters followed by intraocular lens implantation in the capsular bag.

We compared the efficacy of sewing needle microcapsulotomy in preventing Argentinian flag sign with the known small needle aspiration technique in 20 cases of intumescent
white cataracts (n = 10 in each group). Cases were randomly allotted to each group and were single blinded. All surgeries were, performed by a single surgeon in a single surgical setup. We found that none of the cases developed Argentinian flag sign where we used the sewing needle microcapsulotomy to puncture the taut anterior capsule. A smooth round microcapsulotomy was created in a single attempt in all cases and bag was sufficiently decompressed. In none of the cases was the capsulorhexis margin lost during the completion of rhesis later. While using the small needle aspiration technique, in 6 cases the Argentinian flag sign was noted as soon as the sharp hypodermic needle was used to prick the anterior capsule, even before aspiration of lens fluid was attempted. In 2 cases out of the 4 where aspiration was possible, partial splitting and widening of anterior capsular opening was noted which was later converted into a round capsulorhexis with significant manipulation and loss of surgical time. The statistical analysis suggested that sewing needle microcapsulotomy is a safe, simple and effective technique to avoid Argentinian flag sign in intumescent white cataracts (p = 0.011).

<table>
<thead>
<tr>
<th>Technique</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sewing Needle Microcapsulotomy, n=10</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Small Needle Aspiration, n=10</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

P = 0.011

Table 1:
DISCUSSION

The Argentinian flag sign can complicate a surgery for intumescent white cataract during early surgical steps. The widely accepted recommendation to prevent Argentinian flag sign till date involves attempting to decompress the capsular bag by pricking it with a 26 G or 30 G sharp hypodermic needle followed by aspiration of liquified lens matter. This was based on the known fact that raised intralenticular pressure leading to forward nuclear thrust is solely responsible for splitting of the capsule.

We have demonstrated here that it is the sharp tip hypodermic needle, routinely used to puncture the capsule, which has been triggering the mechanism for Argentinian flag sign even before the raised intralenticular pressure comes into play. The linear cut produced by the sharp tip hypodermic needle on a stretched out anterior capsule always has a tendency to open up and extend towards the periphery along its open margins, forming the Argentinian flag sign.

An ideal instrument to open up the tense capsule in intumescent cataracts would be the one which creates a round opening with smooth margins, in real sense a capsulotomy, so that the margins hold resistance against the ensuing forward thrust, hence preventing capsular splitting. The simple yet highly effective tool, sewing needle microcapsulotome has been designed to create a single or multiple microcapsulotomies on the anterior capsule to decompress the bag. Additional manoeuvres like milking out the liquified lens matter through the microcapsulotomies using a visco-cannula can be performed for further decompression. Thereafter the capsulorhexis can be completed as done routinely.

The sewing needle microcapsulotomy technique, along with a new understanding of the factors responsible for Argentinian flag sign, will help the surgeons tackle intumescent white cataract surgeries with confidence.
WHAT WAS KNOWN:

In intumescent white cataracts spontaneous peripheral extension of the initial tear created on anterior capsule by sharp tip hypodermic needle leads to Argentinian flag sign.

Till date it was known that the raised intralenticular pressure leading to forward thrust of the nucleus is solely responsible for the extension of the tear to periphery, to counter which small needle aspiration techniques had been described.

In spite of using needle aspiration techniques, the Argentinian flag sign is known to occur while pricking the capsule, even before attempting to aspirate liquified lens material, thus suggesting a role of factors other than just raised intralenticular pressure.

WHAT THIS PAPER ADDS:

In intumescent white cataracts, it is primarily the 'linear cut' configuration of the initial prick made by sharp hypodermic needle on the anterior capsule, which has the potential to spontaneously extend along its open edges aided by raised intralenticular pressure, leading to Argentinian flag sign.

The technique of sewing needle microcapsulotomy creates an opening in the anterior capsule which has a round regular configuration, like a capsulotomy in true sense, that provides resistance against the disruptive force triggered by the high intralenticular pressure, thus preventing Argentinian flag sign.

This simple yet highly effective novel tool- sewing needle microcapsulotome creates single or multiple microcapsulotomies to adequately decompress the bag prior to the initiation of capsulorhexis.
REFERENCES


Can Stereoacuity Replace Visual Acuity In Amblyopia Risk Factor Screening Among Pre-Schoolers?

Dr. Sanitha Sathyan

ABSTRACT:

AIM:
To compare the efficacy of preschool visual acuity charts (Lea Symbols/ HOTV) with TNO stereoacuity chart for the detection of amblyopia risk factors among preschoolers.

METHODS:
In this comparative observational study, 634 preschoolers between 3 to 6 years of age underwent screening using TNO near stereoacuity and Lea symbols / HOTV charts and the screening efficacy was analyzed using Chi Square test.

RESULTS:
The methods agreed in 537 (87.70 %) children and did not agree in 97 (15.30 %). In the total population, 48 children (7.57 %) missed in visual acuity screening were detected by TNO test (p = 0.00). Forty-nine children (7.72 %) who were missed in TNO test were detected by visual acuity screening (p = 0.00). Age wise comparisons between detection
rates of the two tests were also significant: 3 years (p = 0.005), 4 years (p = 0.007), 5 years (p = 0.002) and 6 years (p = 0.00).

CONCLUSION:

Combination of visual acuity and stereoacuity screening is the preferred intervention. As standalone, TNO is preferred in the 3 and 4-year-olds. In 5 and 6-year-olds, either of the tests can be used with comparable screening efficacy.

INTRODUCTION:

Preschool vision screening is an important public health intervention aimed at timely detection of amblyopia and its risk factors. The United States Preventive Task Force recommends screening all children between 3 to 5 years to detect amblyopia and its risk factors (1,2) as they are old enough to co-operate and within the window for effective interventions. (3)

Screening for risk factors of amblyopia among preschool children is challenging. Conventional methods of screening involve distance visual acuity estimation using age-appropriate visual acuity charts. Popular among these are Lea Symbols chart, HOTV chart etc. Visual acuity estimation using these charts requires good comprehension, relatively good attention span and skills for naming/matching the optotypes. This is also a resource/labor intensive and time-consuming procedure, to be done by trained professionals. (4,5,6) Though useful for large scale screening, vision screeners and photorefractors, are more expensive and may not be viable in smaller eye care facilities and in developing countries. (3)

Stereoacuity tests measure the quality of binocular vision. In potentially amblyogenic conditions like childhood refractive errors, strabismus and media opacities, binocular vision fails to develop normally. This failure in binocular vision development can be detected even in young children, who may not co-operate for formal screening with conventional visual acuity charts used for pre-school children.
This study was done to compare the efficacy of amblyopia risk factor screening using near stereoacuity chart and pre-school visual acuity charts, among preschoolers in an urban setting.

AIM:

Aim of this study is to compare the efficacy of visual acuity screening using Lea Symbols / HOTV charts and TNO stereoacuity chart, in screening for amblyopia and its risk factors among preschool children, between 3 to 6 years of age.

METHODS:

In this comparative observational study, a total of 702 children from 12 preschools in an urban locality were enrolled. The study was done as a part of the preschool outreach screening conducted by a tertiary care eye facility and the study period was from November 2019 to January 2020. All children between 3 and 6 years of age, who succeeded the pre-test and from whom reliable screening measurements could be obtained were included in the study. Those with unreliable measurements, neurological deficits, mental retardation, and multiple disabilities were excluded. The study adhered to the tenets of the Declaration of Helsinki and informed consent letter was obtained from parents/guardians of all children before the screening procedure.

PROCEDURE:

All the participants were tested at the preschool premises during the working hours, in a dedicated space with illumination more than 300 lux. Near stereoacuity screening was done first in all patients to avoid the effect of mono-ocular occlusion on stereoacuity values. Near stereoacuity testing was explained to each child using a single stereogram card with a “popping out” cartoon image. After familiarizing the child with the concept of stereovision, near stereoacuity estimation was formally done. TNO stereo test (Lameris Intrumenten, Groenekan, the Netherlands, 10th edition), held at a distance of 40 cm was
used for near stereoacuity estimation. After wearing red/green anaglyph stereo glasses, the child was first presented with plate I and the response was recorded. When correct response was obtained, plates II and III were shown. After this threshold stereoacuity measures were obtained using plates V–VII and levels of disparity from 480, 240, 120, 60, 30, and 15 arc sec were tested and the results recorded. Those children who could identify the level of disparity corresponding to 240 sec of arc were denoted as ‘pass’ and those who could not identify it were denoted as ‘fail.’

Pretesting using Lea Symbols chart (LS) / HOTV chart (HOTV) was done to ascertain whether the child could identify the optotypes. A card with a single large symbol in LS or letter in HOTV was held at 60 cm from the child and the child was instructed to match the optotype with the key card. This was repeated for the four symbols and six letters and a maximum of two chances to respond were given. Only those children who responded correctly were selected for further examinations and others were excluded.

Those who passed the pretest underwent formal vision screening using Lea Symbols Chart (LS 10-line folding pediatric eye chart and key card (250200, Good-Lite Co; Elgin, IL) and HOTV and the corresponding key cards (2204-P-1004, Keeler, Windsor, The United Kingdom). The examination distance was 3 meters. Right eye was tested first followed by the left eye.

Testing with Lea Symbols was initiated at a line where the child instantly recognized the optotypes. Only when the first three optotypes at a particular level were answered correctly, was the next higher line introduced. If only two of the three symbols were answered correctly in a particular line, was the fourth symbol asked. If correct response was obtained, the examiner proceeded to the next line. If there were fewer than three correctly identified optotypes in a particular line, the previous line was taken as the visual acuity estimate. With HOTV chart, children who could identify all the letters in a row were tested for the next line. If the child could not identify all the letters in a line, the
value of the previous line was considered as the visual acuity. Visual acuity cut off score for both the charts was taken as the line corresponding to 0.4 logMAR for 3-year-olds, 0.3 logMAR for 4-year-olds, 0.2 logMAR for 5-year-olds and 0.1 logMAR for 6-year-olds. Those who could identify the cutoff line were denoted as 'pass' and those who failed were denoted as 'fail.'

All the children underwent corneal reflex test, evaluation of ocular movements, cover test, non-mydriatic retinoscopy and flash light examination. Those who failed any of these tests were referred to the base hospital for detailed evaluation.

**STATISTICAL ANALYSIS:**

Statistical analysis was performed using SPSS software for Windows version 20.0 (SPSS Inc., Chicago, Illinois, USA). Descriptive tests were used to analyze the visual acuity and stereoacuity estimate. The Chi Square was used for significance testing and \( p < 0.05 \) was taken as significant.

**RESULTS:**

Of the 702 children enrolled, 634 (90.31 \%) children who were judged by the observers as successfully comprehending the pre-tests for visual acuity and stereoacuity were included in the final analysis. Sixty-eight (9.69 \%) children who failed to comprehend/respond to the pre-tests were excluded. Out of the 634 children in the final sample, 33 children (5.21 \%) were 3 years of age, 63 (9.94 \%) were 4 years of age, 203 (32.02 \%) were 5 years of age and 335 (52.84 \%) were 6 years of age. There were 322 males (50.79 \%) and 312 females (49.21 \%).

The mean visual acuity was 0.18 ± 0.08 logMAR in 3-year-olds, 0.17 ± 0.04 logMAR in 4-year-olds, 0.08 ± 0.02 logMAR in 5-year-olds and 0.06 ± 0.02 logMAR in 6-year-olds. The mean near stereoacuity estimated was 747.00 ± 134.22 sec of arc in 3-year-olds, 306.88 ± 95.42 sec of arc in 4-year-olds, 197.44 ± 233.91 in 5-year-olds and 263.58 ± 189.37 in 6-year-olds.
Using the criteria for ‘pass’ and ‘fail’ 8 patients (24.24%) of the 3-year-olds, 6 patients (9.52%) of the 4 year olds, 29 (14.29%) of the 5 year olds and 42 (12.54%) of the 6 year olds, failed the visual acuity screening. Using the TNO stereoacuity cut off, 14 patients (42.42%) of the 3-year-olds, 11 patients (17.46%) of the 4 year olds, 28 (13.79%) of the 5 year olds and 31 (9.25%) of the 6 year olds failed the stereoacuity screening. (Table: 1)

<table>
<thead>
<tr>
<th>Age</th>
<th>Mean presenting visual acuity</th>
<th>Mean stereoacuity (sec of arc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 years</td>
<td>0.18 ± 0.08 logMAR</td>
<td>747.00 ± 134.22</td>
</tr>
<tr>
<td>4 years</td>
<td>0.17 ± 0.04 logMAR</td>
<td>306.88 ± 95.42</td>
</tr>
<tr>
<td>5 years</td>
<td>0.08 ± 0.02 logMAR</td>
<td>197.44 ± 233.91</td>
</tr>
<tr>
<td>6 years</td>
<td>0.06 ± 0.02 logMAR</td>
<td>263.58 ± 189.37</td>
</tr>
</tbody>
</table>

**Table: 1** Mean visual acuity and stereoacuity estimates

<table>
<thead>
<tr>
<th>Age group</th>
<th>TNO fail</th>
<th>TNO pass</th>
<th>Total</th>
<th>P-value (Chi Square test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 years Visual acuity fail</td>
<td>7</td>
<td>1</td>
<td>8</td>
<td>0.005</td>
</tr>
<tr>
<td>Visual acuity pass</td>
<td>7</td>
<td>18</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>19</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>4 years Visual acuity fail</td>
<td>4</td>
<td>2</td>
<td>6</td>
<td>0.007</td>
</tr>
<tr>
<td>Visual acuity pass</td>
<td>7</td>
<td>50</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>52</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>5 years Visual acuity fail</td>
<td>10</td>
<td>19</td>
<td>29</td>
<td>0.002</td>
</tr>
<tr>
<td>Visual acuity pass</td>
<td>18</td>
<td>156</td>
<td>174</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>175</td>
<td>203</td>
<td></td>
</tr>
<tr>
<td>6 years Visual acuity fail</td>
<td>15</td>
<td>27</td>
<td>42</td>
<td>0.000</td>
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<tr>
<td>Visual acuity pass</td>
<td>16</td>
<td>277</td>
<td>293</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>304</td>
<td>335</td>
<td></td>
</tr>
<tr>
<td>Total Visual acuity fail</td>
<td>36</td>
<td>49</td>
<td>85</td>
<td>0.000</td>
</tr>
<tr>
<td>Visual acuity pass</td>
<td>48</td>
<td>501</td>
<td>549</td>
<td></td>
</tr>
<tr>
<td></td>
<td>84</td>
<td>550</td>
<td>634</td>
<td></td>
</tr>
</tbody>
</table>
The screening outcome according to the pass/fail criteria (visual acuity charts based/TNO stereoacuity based) agreed in 537 (87.70 %) children; but did not agree in 97 (15.30 %) children. In the total population, 48 (7.57 %) children who failed the visual acuity screening, passed the TNO screening, and 49 (7.73 %) children who failed in visual acuity test passed the TNO test (Figure: 1).

Subgroup analysis was done as the younger age group (3 and 4 years) and the older age group (5 and 6 years). In the younger age group (3 and 4 years), methods agreed in 79 (82.29 %) children and did not agree in 17 (17.71 %). Among the 3-year-olds, 25 (75.76 %) children would have the same screening outcome if either of the tests was used, 8 (24.24 %) would have different outcome with the tests. In the 4-year-olds, 54 (85.71 %) children would have the same outcome if either test was used for screening, and 9 (14.29 %) would have different outcome.

In the older age group (5 and 6 years), methods agreed in 457 (84.94 %) patients and did not agree in 80 (14.87 %) children. Among the 5-year-olds, 166 (81.77 %) children would have the same outcome if either test was used for screening, and in 37 (18.23 %) the outcome would have been different. In the 6-year-olds, 292 (87.16 %) children would have the same outcome if either test was used for screening, 43 (12.84 %) would have different outcomes.
Among the 3-year-olds, 8 (24.24%) children would be referred for further evaluation if visual acuity screening criteria alone was used and 14 (42.42%) children would be referred if TNO test screening criteria alone was used. In the 4-year age group, 6 (9.52%) children would be referred for further evaluation if visual acuity screening criteria alone was used and 11 (17.46%) children would be referred if TNO test screening criteria alone was used. The referral rates would be 29 (14.29%) and 28 (13.79%) in the 5-year age group and 42 (12.54%) and 31 (9.25%) in the 6-year-old age group, for visual acuity screening and stereoacuity screening respectively. Figure: 2 represents the referral rates by the visual acuity and stereoacuity screening criteria.

Figure: 2 Referral rates by visual acuity and stereoacuity tests

When a single screening test (visual acuity/near stereoacuity) alone was used for screening the detection rates varied across all age groups. In the 3-year-old age group, 7 (21.21%) children who would have missed referral in visual acuity test, were detected as referral by TNO test. Similarly, in the 4-year age group, 7 (11.11%) children who would have missed
referral in visual acuity test, would be detected by TNO test. In the 5-year-old group, 18 (8.87 %) children who would have been missed referral in visual acuity test would be detected by TNO test and 16 (4.78 %) children in the 6-year age group who would be missed in visual acuity test would be detected by TNO test.

In similar lines, in the 3-year-old age group, 1 (3.03 %) child who would have missed referral in TNO test, was detected as referral by visual acuity test. Similarly, in the 4-year age group, 2 (3.17 %) children who would have missed referral in TNO test, would be detected by visual acuity test. In the 5-year-old group, 19 (9.36 %) children who would have been missed referral in TNO test would be detected by visual acuity test and 27 (8.06 %) children in the 6-year age group who would be missed in TNO test would be detected by visual acuity test.

48 (7.57 %) children in the whole sample were missed in visual acuity test but detected by TNO test; 49 (7.72 %) were missed in TNO test but detected by visual acuity test. (Table: 3)

<table>
<thead>
<tr>
<th></th>
<th>Missed in Visual acuity screening, detected in TNO screening</th>
<th>Missed in TNO screening, detected by visual acuity screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 years</td>
<td>7 (21.21%)</td>
<td>1 (03.03%)</td>
</tr>
<tr>
<td>4 years</td>
<td>7 (01.11%)</td>
<td>2 (03.17%)</td>
</tr>
<tr>
<td>5 years</td>
<td>18 (08.87%)</td>
<td>19 (09.36%)</td>
</tr>
<tr>
<td>6 years</td>
<td>16 (04.78%)</td>
<td>27 (08.06%)</td>
</tr>
<tr>
<td>total</td>
<td>48 (07.57%)</td>
<td>49 (07.72%)</td>
</tr>
</tbody>
</table>

Table 3: Percentage of children missed if a single screening test alone was used
If the visual acuity and stereoacuity tests were used in combination, 36 children (5.68%) in the total population would fail the tests and be eligible for referral. Categorizing age wise, this means 7 children (21.21%) in the 3 year age group, 4 children (6.34%) in the 4 year age group, 10 children (4.93%) in the 5-year age group and 15 children (4.48%) in the 6 year age group would fail the combination of tests and be eligible for referral (figures: 4).

**DISCUSSION:**

In our study, there was significant difference between the referral rates detected by visual acuity based charts and TNO stereoacuity chart in the whole population \( (p = 0.00) \) and also in each of the age groups (3 years: \( p = 0.005 \), 4 years: \( p = 0.007 \), 5 years: \( p = 0.002 \), 6 years: \( p = 0.00 \)). The two methods showed disagreement in 97 (15.30%) children. This is a significant proportion and indicates that these children may be detected falsely as ‘normals’ and may be not be advised referral examination. In these children, detection of amblyopia risk factors and management may be delayed.

In the 3 and 4 year olds, TNO was better than visual acuity charts in detecting amblyopia and its risk factors. It is established that preschool vision screening with distance visual
acuity estimation can reliably detect myopia, but may miss moderate hyperopia and significant astigmatism.\(^{(7,8)}\) Hyperopia which has more potential for the development of amblyopia than myopia, is more common in younger children.\(^{(10,11)}\) Moreover, undetected hyperopia is associated with reduced visuo-cognitive ability, reading ability, and visual attention in young children.\(^{(12,13,14)}\) Though non-mydiatic retinoscopy values, which is considered as the gold standard of preschool screening, were not included in the purview of this study, we assume that the possibility of higher prevalence of hyperopia among the younger children would have resulted in better detection rates by TNO.

Strabismus and media opacities, which have high potential for the development of amblyopia, cause early impairment of binocular vision. This drift can happen even before amblyopia can be picked up with conventional vision charts.\(^{(11)}\) Stereoacuity tests are more effective in detecting subtle amblyopia and strabismus compared to refractive or visual acuity screening tests, and correlate with the degree of visual loss.\(^{(17)}\) They also have the advantages of being less demanding in terms of time and attention span. These factors and the easy testability of TNO stereotest would also have contributed to the higher detection rates in TNO test.

The inherent drawbacks of pre-school visual acuity charts like the need for good comprehension, attention span, hand-eye co-ordination, skills for matching/naming the optotypes and cultural specificity of the optotypes may have interfered with the visual acuity estimation in younger children (3 and 4 years). However, in the older age group (5 and 6 years), detection rates of visual acuity and TNO stereoacuity were comparable. This may be due to the improved attention span and the gradual shift towards emmetropization around 6 years of age.

Our study suggests that ‘pass’ in the distance visual acuity screening test or TNO stereotest alone does not eliminate the need for further evaluation of visual status.\(^{(7)}\) Though TNO was definitely better in the younger age groups, the detection rates were equivocal in the older age groups. Combined screening using both the tests reduced the false referral rates
and false non-referrals (figure: 4). Therefore, we suggest that combination of visual acuity and stereoacuity test is to be done whenever possible in preschool population as it has better detection rates than standalone tests. If the combination cannot be performed in younger children due to their short attention span, TNO test is better as it has better detection rates in the younger age groups. This can lead to ‘over referrals’ for cycloplegic retinoscopy and detailed evaluation, but is desirable than missing children (false non-referrals) who need further evaluation for amblyopia risk factors. In the older age group (5 and 6 year olds), the outcomes of screening using visual acuity charts and TNO Chart was equivocal. Combined screening using the two methods reduced false referrals and false non-referrals across all the age groups.

**CONCLUSION:**

The present study shows that combination of visual acuity screening (using Lea Symbols and HOTV pre-school visual acuity charts) and stereoacuity screening (using TNO chart) is the preferred intervention in preschoolers between 3 to 6 years of age for detecting amblyopia and its risk factors. If combining the tests is difficult in the younger age group (3 and 4 year old), TNO is preferred over visual acuity estimation. In older children (5 and 6 years), either of the tests can be used with comparable screening efficacy.

**REFERENCES:**


Opportunistic Screening Of Ametropia And Amblyogenic Factors In Children Using Brückner Test.

Dr. Mihir Trilok Kothari, Dr. Sai Deshpande

INTRODUCTION

The American Academy of Pediatrics currently recommends red reflex assessment as a component of the eye evaluation in the neonatal period and during all subsequent routine health supervision visits. The red reflex test also called Brückner test aims to identify opacities in the visual axis and pathologies of the posterior segment. It diagnoses the common causes of childhood blindness that includes congenital cataract, undiagnosed amblyopia, retinoblastoma and corneal opacities. However Brückner test can also be used to assess other amblyogenic factors namely ametropia, anisometropia and squint, especially in preverbal children. In the hospital based settings the sensitivity of the Brückner test was 87.5 % and speciﬁcity 84.1 %; the positive (PPV) and negative predictive (NPV) value was 71.8 % and 93.6 % making the test a useful, ultralow cost, rapid screening tests in the hands of the Optometrist and the Pediatric Ophthalmologist. In a population based screening program, the test was found useful for the screening in the hands of the Pediatrician.
Since red reflex test is anyways mandated as per the preferred practice guidelines for the Pediatricians as a routine screening test for preverbal children, we decided to evaluate the reliability of Brückner test in the hands of a Pediatric resident in a routine hospital based Pediatric OPD (outpatient department).

**SUBJECTS AND METHODS:**

The study was carried out in the outpatient Pediatric department of Jupiter hospital, Thane

After obtaining permission from the institutional ethics committee. Ten percent of all eligible children presenting in the pediatric outpatient department of Jupiter Hospital between 1 - 16 years of age, of both sexes and whose parents had signed written informed consent were included. Children with the history of ocular surgery, nystagmus, clinically visible strabismus, congenital anatomical abnormalities of eye, poor general condition and uncooperative patients were excluded.

The data was entered in the MS-Excel-2010 and analysed using SPSS-16 software. The test was evaluated using 2x2 Bayesian Table and the interrater reliability was analysed using the Kappa statistic. The P value less than 0.05 was taken as statistically significant.

To check the validity, various parameters like sensitivity, specificity, positive predictive value & negative predictive value & accuracy were calculated.

1. The Pediatric resident was trained to detect red reflex abnormalities in children by teaching optics of red reflex testing using didactic lecture and simulation on a dummy eye. The resident was asked to perform the technique (monocular, binocular and dynamic) on patients alongside with a trained Pediatric Ophthalmology fellow.
2. Initially the red reflex test was performed by the trained Pediatric resident on children fulfilling the inclusion and exclusion criteria in the Pediatric Outpatient Department using an ophthalmoscope (Heine Germany Beta 200) at a distance of one meter.

3. Both eyes were illuminated simultaneously by ophthalmoscope with the child looking at a distant object six meters away and the lens dial was adjusted till the pupillary red reflex was focused.

4. Presence of any media opacities, difference in colour of red reflex, anisocoria, leukocoria was noted.

5. Presence of amblyogenic factors like squint, anisometropia were noted.

6. The position and size of pupillary crescent was noted and labelled as: emmetropia (normal crescent), hypermetropia (hypermetropic crescent), myopia (myopic crescent) to detect abnormalities of refraction.

7. Presence or absence of astigmatism was noted based on the position of the pupillary crescent.

8. Dynamic Distant Direct Ophthalmoscopy for testing accommodation was done and any accommodation failure was ruled out.

9. Any other eye abnormalities during red reflex testing was noted.

10. Results of red reflex testing was labelled as pass if normal and fail if any abnormality was noted in the red reflex testing of either eye each by the Pediatric resident and Pediatric Ophthalmology fellow.

11. Retinoscopic measurements obtained using an automated Photoscreener in a dark room was noted for both eyes and was labelled as pass if normal and fail if abnormal (according to the American Academy of Pediatrics - Preferred practice guidelines for correction of refractive errors in children and GPOS criteria)
12. Cycloplegic refraction was done 30 minutes after instilling short-acting cycloplegic and compared with the findings of the Optometrist (post cycloplegic refraction/retinoscopic findings).

13. Post cycloplegic retinoscopic measurements of the Optometrist was noted for both eyes and was labelled as Pass if normal, Fail if abnormal (according to the American Academy of Pediatrics Preferred practice guidelines for correction of refractive errors in children and GPOS criteria).

<table>
<thead>
<tr>
<th>Refractive Error</th>
<th>Pattern of Crescent</th>
<th>Size of Crescent</th>
<th>True Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myopia</td>
<td>Inferior crescent</td>
<td>&gt;1 mm</td>
<td>&gt;= -1 D</td>
</tr>
<tr>
<td>Astigmatism</td>
<td>Crescent anywhere</td>
<td>&gt;1 clock hour decentered</td>
<td>&gt;= 1.5 D</td>
</tr>
<tr>
<td>Hypermetropia</td>
<td>Superior crescent</td>
<td>&gt;= 2 mm</td>
<td>&gt;= 1D</td>
</tr>
<tr>
<td>Emmetropia</td>
<td>Superior crescent</td>
<td>&lt; 2 mm</td>
<td>&lt; 1D</td>
</tr>
</tbody>
</table>

Table 1. Cut off values for crescent measurement and cycloplegic refraction 2

<table>
<thead>
<tr>
<th>AGE</th>
<th>Isometropia</th>
<th>Myopia</th>
<th>Hypermetropia</th>
<th>Hypermetropia with esotropia</th>
<th>Astigmatism</th>
<th>Anisometropia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age 1 to &lt;2 years*</td>
<td>Age 2 to &lt;3 years*</td>
<td>Age 3 to &lt;4 years*</td>
<td>Age 4 years and more#</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myopia</td>
<td>4.00 D or more</td>
<td>3.00 D or more</td>
<td>2.50 D or more</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypermetropia</td>
<td>5.00 D or more</td>
<td>4.50 D or more</td>
<td>3.50 D or more</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypermetropia with esotropia</td>
<td>2.00 D or more</td>
<td>1.50 D or more</td>
<td>1.50 D or more</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astigmatism</td>
<td>2.50 D or more</td>
<td>2.00 D or more</td>
<td>1.50 D or more</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anisometropia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Criteria for refractive error correction in children
American Academy of Pediatrics Preferred Practice Pattern guidelines criteria for refractive errors in Children

#GPOS (Group of Pediatric Ophthalmologists and Strabismologists), Mumbai criteria

The result of Kappa were interpreted as follows:

- < 0.2 – Negligible agreement
- 0.2 - 0.4 – Minimal agreement
- 0.4 - 0.6 – Fair agreement
- 0.6 - 0.8 – Good agreement
- > 0.8 – Excellent agreement

RESULTS:

Total 120 children were examined by all 4 observers. The mean age was 5.2 yrs (1-15 yrs.).

<table>
<thead>
<tr>
<th>SEX</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>61</td>
<td>50.8</td>
</tr>
<tr>
<td>Male</td>
<td>59</td>
<td>49.2</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 3: Gender Distribution of the Participants of study

Image 1: Gender distribution of the study participants
Table 4: screening results by observers

<table>
<thead>
<tr>
<th></th>
<th>Pediatrician</th>
<th>Ophthalmologist</th>
<th>Photoscreener</th>
<th>Optometrist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pass</td>
<td>51 (42.5%)</td>
<td>61 (50.0%)</td>
<td>77 (64.2%)</td>
<td>85 (70.8%)</td>
</tr>
<tr>
<td>Fail</td>
<td>69 (57.5%)</td>
<td>59 (49.2%)</td>
<td>43 (35.8%)</td>
<td>35 (29.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>120</td>
</tr>
</tbody>
</table>

Image 2: Screening results by the participants
K = 0.341 (Minimal agreement)  P < 0.001 (Significant) (Cohen's kappa coefficient)

<table>
<thead>
<tr>
<th></th>
<th>Optometrist</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fail</td>
<td>Pass</td>
</tr>
<tr>
<td>Pediatric Resident</td>
<td>Fail</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>88.6%</td>
<td>44.7%</td>
</tr>
<tr>
<td></td>
<td>Pass</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>11.4%</td>
<td>55.3%</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Table 5: Comparison between Pediatric Resident and Optometrist (Gold standard–post cycloplegic retinoscopy) findings

<table>
<thead>
<tr>
<th></th>
<th>Optometrist</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fail</td>
<td>Pass</td>
</tr>
<tr>
<td>Pediatric Resident</td>
<td>Fail</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>88.6%</td>
<td>44.7%</td>
</tr>
<tr>
<td></td>
<td>Pass</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>11.4%</td>
<td>55.3%</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Table 6: Comparison between findings of Ophthalmologist and Optometrist (Gold standard – post cycloplegic retinoscopy)
K = 0.341 (Minimal agreement)  P < 0.001 (Significant) (Cohen’s kappa coefficient)

When both the decisions were compared, it was shown that overall agreement was 70% with simple kappa value 0.396 (Minimal agreement) which was statistically significant (p<0.001).

<table>
<thead>
<tr>
<th>Optometrist</th>
<th>Fail</th>
<th>Pass</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photo screener</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fail</td>
<td>30</td>
<td>13</td>
<td>43</td>
</tr>
<tr>
<td>85.7%</td>
<td>15.3%</td>
<td>35.8%</td>
<td></td>
</tr>
<tr>
<td>Pass</td>
<td>5</td>
<td>72</td>
<td>77</td>
</tr>
<tr>
<td>14.3%</td>
<td>84.7%</td>
<td>64.2%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>85</td>
<td>120</td>
</tr>
<tr>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

Table 7: comparison between findings of photoscreener and optometrist (gold standard-post cycloplegic retinoscopy)

K = 0.660 (Good agreement)  P < 0.001 (Significant) (Cohen’s kappa coefficient)

When both the decisions were compared, it was shown that overall agreement was 85% with simple kappa value 0.660 (Good agreement) which was statistically significant (p < 0.001).
K = 0.667 (Good agreement) P < 0.001 (Significant) (Cohen’s kappa coefficient)

When both the decisions were compared, it was shown that overall agreement was 83% with simple kappa value 0.667 (Good agreement) which was statistically significant (P < 0.001).

<table>
<thead>
<tr>
<th></th>
<th>Pediatric</th>
<th>Ophthalmologist</th>
<th>Photo screener</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>88.6</td>
<td>82.9</td>
<td>85.7</td>
</tr>
<tr>
<td>Specificity</td>
<td>55.3</td>
<td>64.7</td>
<td>84.7</td>
</tr>
<tr>
<td>PPV</td>
<td>44.9</td>
<td>49.2</td>
<td>69.8</td>
</tr>
<tr>
<td>NPV</td>
<td>92.2</td>
<td>90.2</td>
<td>93.5</td>
</tr>
<tr>
<td>Accuracy</td>
<td>65.0</td>
<td>70.0</td>
<td>85.0</td>
</tr>
</tbody>
</table>

Table 9: Comparison of screening results of Pediatrician, Ophthalmologist & Photo screener with Optometrist

Image 3: Comparison of screening results of Pediatrician, Ophthalmologist and Photo screener with Optometrist
DISCUSSION

Red reflex examination in routine Pediatric practice is a very simple, low cost and effective way to screen children for eye diseases. Our study aimed at assessing the validity and precision of red reflex testing performed by a trained Pediatric resident to screen eye diseases in children aged between 1-16 years presenting to Pediatric outpatient department. We studied 120 children who came to the Pediatric outpatient department from 1/3/2019 to 30/4/2019. All 120 children were examined by all 4 observers. The mean age was 5.2 yrs. In our study, majority were females 61 (50.2 %) and 59 (49.8 %) were male. Red reflex test could be completed for all recruited subjects. The time taken to complete this test was approximately 2 minutes per subject.

The Pediatrician identified 69 subjects had failed the red reflex testing and 51 had passed the red reflex test [ Table 8 ] as compared to the Ophthalmologist findings in which 59 subjects had failed and 61 subjects had passed the red reflex test.When both the decisions were compared it was shown that overall agreement was 83% with simple kappa value 0.667 (good agreement) which was statistically significant (p <0.001) [Table 8].

<table>
<thead>
<tr>
<th>Ophthalmologist</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fail</td>
<td>54</td>
</tr>
<tr>
<td>91.5%</td>
<td>57.5%</td>
</tr>
<tr>
<td>Pass</td>
<td>5</td>
</tr>
<tr>
<td>8.5%</td>
<td>42.5%</td>
</tr>
<tr>
<td>Total</td>
<td>59</td>
</tr>
<tr>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Table 8: comparison between findings of Pediatric resident and Ophthalmologist.
K = 0.667 (Good agreement)  \( P < 0.001 \) (Significant) (Cohen’s kappa coefficient)

When both the decisions were compared, it was shown that overall agreement was 83% with simple kappa value 0.667 (Good agreement) which was statistically significant \( (P < 0.001) \).

The red reflex test done by a trained Pediatric resident had a sensitivity of 88.57% \( (95\% \text{ confidence interval - 73.2 \% , 96.80 \%}) \) and specificity of 55.29% \( (95\% \text{ confidence interval - 44.11 \% , 66.09 \%}) \) as compared to the red reflex testing done by trained Pediatric Ophthalmology fellow with sensitivity of 82.9% \( (95\% \text{ confidence interval - 66.35 \% , 93.44 \%}) \) and specificity of 64.71% \( (95\% \text{ confidence interval - 53.59 \% , 74.77 \%}) \) when the results of both observers were compared with the post cycloplegic retinoscopy findings of the Optometrist (gold standard) [Table 5 and Table 6]. The red reflex test in the hands of the trained Pediatric resident and that of trained Ophthalmology fellow had high negative predictive value of 92.2% and 90.2% respectively. We could conclude that red reflex test done by a Pediatric resident is fairly sensitive and has high negative predictive value making it a good screening test to detect eye diseases in routine Pediatric practice by a Pediatrician.

Mihir T Kothari et al studied the use of Brückner test as a rapid screening test to detect significant refractive errors in children. Ninety-six subjects were examined. The Ophthalmologist identified 131 eyes as ametropic and 61 eyes as emmetropic. The Brückner test had sensitivity 91%, specificity 72.8%, positive predictive value 85.5% and negative predictive value 83.6% which was similar to the results of our study.

Jalis M et al also used the Brückner test for the detection of significant refractive errors in children. Brückner test was performed in children upto 15 years of age with a direct Ophthalmoscope and the position and size of pupillary crescent was noted. Subsequently, noncycloplegic and cycloplegic auto-refraction was performed using auto-refractometer.
The results were published in the Journal of Rawalpindi Medical College. 2015 Dec 30;19(3):200-3.

Saiju R et al in their study measured the effectiveness of the Brückner red reflex test for screening of posterior segment opacities in children. Patients with abnormal Brückner tests had their eyes dilated for further investigations. 172 patients (97 boys and 75 girls) were included in the study. Twenty-three had abnormal Brückner test results in either one or both eyes. The specificity of this test was 98.7%. The screening test had a positive predictive value of 90.5% and a negative predictive value of 97.4%. The study concluded that Brückner test screening is a sensitive and specific marker for detecting the posterior segment opacities in children, and recommended utilizing the test to evaluate these problems where other technologies are rare. The results were published in the Kathmandu University Medical Journal. 2012;10 (2):23-6.

In our study of 120 patients, the retinoscopy findings of the photoscreener when compared with that of the optometrist (gold standard) showed a sensitivity of 85.7% (95% confidence interval -69.74%, 95.19%) specificity of 84.71% (95% confidence interval -75.27%, 91.60%) and a negative predictive value of 93.51%.[Table 7]. This showed that the photoscreener is superior in detecting refractive errors & astigmatism in children as compared to manually performed red reflex testing done by the trained Pediatric resident.

Paysse EA et al studied the ability of Pediatric residents to differentiate an asymmetric from a symmetric red reflex in patients with anisometropia and microstrabismus using the Brückner reflex and the Medical Technology Innovations (MTI) photoscreener. A prospective, masked, case-control study was performed by twelve Pediatric residents who evaluated 10 study patients and 6 control subjects in a masked manner in 2 separate sessions, using the Brückner reflex or the MTI photoscreener, evaluating for asymmetric (abnormal) or symmetric (normal) red reflexes between the 2 eyes. The pediatric residents
had a mean correct score of 82% (69% – 100%) using the MTI photoscreener versus a mean correct score of 65% (44% – 81%) using the Brückner reflex (McNemar test: < 0.01). The sensitivity of the MTI photoscreener evaluation was 89% in comparison to 61% for the Brückner reflex. The specificities for the MTI photoscreener versus the Brückner reflex were similar at 69% and 71% respectively. They concluded that Pediatric residents were better at detecting asymmetric red reflexes in patients with anisometropia and microstrabismus when evaluating MTI photoscreener photographs than when evaluating the red reflexes by the Brückner reflex. The MTI photoscreener may be a more sensitive method than the Brückner reflex to screen for the common amblyogenic risk factors of anisometropia and microstrabismus by easier detection of red reflex asymmetry. The findings of this study were similar to the findings of our study that automated photoscreening using photoscreeners is a more sensitive and specific as compared to manually performed red reflex testing.

Limitations in our study

1. A major limitation is difficulty in quantifying the results. This difficulty may also cause inter-observer and intra-observer variations.

2. We found that lack of accommodative control and absence of distance fixation target can cause pseudomyopia that can reduce the specificity and predictive value of the positive test.

3. The test is rendered useless with dilated pupil.

4. Though we did not have a patient with high ametropia we are aware that patients with high myopia have a dark fundal glow and patients with high hypermetropia have a bright fundal glow. In both the situations there is an absence of the crescent. The examiner should be aware of this situation and diagnose these patients as having high ametropia.
5. Variability in the pigmentation of the fundus has previously been reported to affect the sensitivity of the Brückner test when used to detect amblyogenic factors—darker fundus pigmentation is associated with lower sensitivity. It is not clear what effect pigmentation of the fundus may have on the Brückner test when used to detect refractive errors.

6. As the Brückner test provides possibilities to introduce lower cutoffs for the crescent size that may improve sensitivity and negative predictive value at the cost of increasing the false positives. We are concerned about the relatively higher false positive cases value obtained for the red reflex testing done by Pediatric resident in our study. The issue of false positives is of importance, as these subjects are referred to Ophthalmologist for more sophisticated and often more expensive tests, placing an additional burden on healthcare programs. This limitation can be overcome with more training and the examiners must decide cutoffs to provide maximum effectiveness to the screening program.

CONCLUSIONS:

Our study on screening of eye diseases using red reflex testing by a Pediatric resident concludes that the photoscreener has a higher specificity and sensitivity in detecting refractive errors and astigmatism as compared to manually performed red reflex testing. But in absence of costly ophthalmic instruments like the photoscreener, red reflex testing is a good screening test in routine Pediatric OPD as it is low cost, less time consuming, can be done with a direct Ophthalmoscope only, is fairly sensitive and has a high negative predictive value.

We conclude that red reflex testing – 1) Is a relatively easy and simple test to administer, 2) Can train persons with no or minimal prior experience 3) Can be administered using
only a direct Ophthalmoscope, thereby minimizing costs when compared to a
photoscreener 4) Can potentially screen a large population within a short period as the
test does not take long to administer 5) The test has good sensitivity 6) With experience
the sensitivity and specificity improves 7) The investigator can proceed with the additional
examination using the same Ophthalmoscope 8) It is a useful test in screening of children
for eye diseases in routine Pediatric practice.
National Survey On Human Resources And Infrastructure For Eye Care Services In India

Dr. Praveen Vashist, Dr. Suraj Singh Senjam, Dr. Vivek Gupta, Dr. Souvik Manna, Dr. Amit Bhardwaj, Dr. Rohit Saxena, Dr. Namrata Sharma, Dr. Promila Gupta

ABSTRACT:

The year 2020 marks the final year for the achievement of targets of the Vision 2020 Right to Sight initiative. The objectives of the study were to determine the human resources and infrastructure available for ophthalmic services, including paediatric services, in secondary and tertiary level hospitals in India, and to determine the achievement of targets related to human resources and infrastructure as per Vision 2020 Right to Sight norms. An online questionnaire was mailed to all eye-institutes of the country and telephonic follow up was done to ensure response. A total of 9440 eye institutes were identified in the country through various yellow pages and available online directories, which were requested for participation in the survey. Out of them, 8790 (93.1%) institutes were contacted telephonically, and remaining institutes could not be contacted of 8790 eye-care institutes, a complete response was obtained from 7901 institutes (response rate 89.9%) and among them 2180 institutes (27.6%) reported to have pediatric eye care services. The number of optometrists per ophthalmologist was 0.85 whereas the ophthalmologist population ratio was found to be 1:65221 in the country. One encouraging
The finding of the survey was 8 paediatric ophthalmologists per 10 million population which is a much more optimistic figure than the minimum requirement of 1 per 10 million.

INTRODUCTION

The elimination of avoidable blindness is the major goal of the World Health Organization (WHO) and the national governments in different countries.\textsuperscript{[1]} The Vision 2020 – Right to Sight initiative is committed to strive for the elimination of major causes of avoidable blindness globally.\textsuperscript{[2]} Childhood blindness is an area of concern of all national and international efforts, especially in developing countries like India.\textsuperscript{[3]} Half of childhood blindness load is amenable to current preventive and curative strategies. In such a situation, it is important to provide comprehensive eye care services to tackle childhood blindness across the country. The WHO estimates that in 2015 there were 253 million people with visual impairment, including 36 million people blind globally.\textsuperscript{[4]} Though the overall prevalence of blindness and visual impairment is much lower in children compared to adults, children need overarching attention because of the number of years that they would live with blindness or impaired vision. The global estimate of children with severe visual impairment and blindness (SVI/BL) is 1.4 million,\textsuperscript{[5]} of whom nearly 300,000 are in India.\textsuperscript{[6]}

Causes of childhood blindness have been estimated from two sources in India. One set of estimates is derived from studies done on children in schools for the blind while the other set is based on population-based studies. Retina, cornea and whole globe have been reported to be the commonest anatomical site for blindness in children in institutional studies,\textsuperscript{[7]} while refractive error and amblyopia were reported to be the commonest causes in population-based studies.\textsuperscript{[8]}

In the Vision 2020 Action plan, the Government of India targets to train 200 ophthalmologists, pediatricians, anesthetists and paramedics in various fields related to paediatric ophthalmology to combat childhood blindness in India.\textsuperscript{[9]} By the year 2020, the Government of India visualizes the development of paediatric ophthalmology units at all
tertiary health care institutions. It was aimed to provide specially trained paediatric eye care personnel at centers established at the norm of 1 per 10 million population.\textsuperscript{[10]}

There is a paucity of data on the availability of services as well as infrastructure to tackle childhood blindness, especially in the public sector. A few studies were conducted more than a decade ago and data was collected from medical colleges and NGO eye hospitals on the infrastructure and human resources for paediatric eye care.\textsuperscript{[11,12]}

Planning effective eye care service delivery systems for children needs baseline data on the availability of eye care services for control of childhood blindness and visual impairment at the tertiary and secondary level. It is also required to obtain the estimates of what proportion of ophthalmologists are currently engaged in providing eye care services to children.

The availability and deployment of trained human resources and the establishment and adequate functionality of available infrastructure are both important for the control of childhood blindness and visual impairment. The objectives of the study were to determine the human resources and infrastructure available for providing ophthalmic services from the existing secondary and tertiary level hospitals in India and to assess the achievement of targets related to human resources and infrastructure as per Vision 2020 Right to Sight norms.

**METHODOLOGY:**

**STUDY SETTING:**

India is a union of 28 states and 9 union territories, having a total of 739 districts. The study was undertaken over one year period from January 2020 to December 2020.

**DEVELOPMENT OF STUDY QUESTIONNAIRE:**

Previous surveys on eye care services were studied and subjected to extensive discussion
and scrutiny by the investigators. This period included January 2020 to March 2020 during which time an extensive phase of qualitative discussions was done to suggest data collection strategies that fit the national context, to verify that all definitions were understood and to investigate internal data discrepancies and non-response fields. Inputs were also obtained from Non-Governmental Organization partners, National Program for Control of Blindness, Government of India, All India Ophthalmic Society and Vision 2020- The Right to Sight India. For the present survey, it was decided to include institutes having at least one ophthalmologist. Hence, vision centres manned by Ophthalmic Assistants were not included in the survey. VISION 2020- The Right to Sight India, targets were used as a benchmark for data on HR while the equipment were selected by a team of expert from the International Agency for Blindness and Prevention list of equipment. The ethical permission for conducting the study was obtained from the Institute Ethics Committee of All India Institute of Medical Sciences New Delhi.

Data were collected in two phases using different strategies as follows:

(i) An online questionnaire-based survey, including paediatric eye facilities using a specially developed questionnaire on Human Resources, Infrastructure, and Equipment

(ii) Online meetings with SPOs (State Program Officers) and DPOs (District Program Officers) in all states/UTs.

For the first phase of data collection, a list of eye care facilities including their physical addresses, telephone numbers and email IDs were first prepared by searching yellow pages and available online directories. Online search was performed using NIC (National Informatics Centre) district portals, Ayushman Bharat Directories along with websites of reputed private hospitals. AIOS (All India Ophthalmological Society) database of ophthalmologists was used to find names and contact details of ophthalmologists in districts. The list was supplemented with information from eye care personnel who knew of other facilities not captured in the initial list. Private-for-profit and non-profit eye care facilities were also included in the search.
Once the baseline database was completed, the survey questionnaire was emailed to respective eye-care facilities for self-completion followed by a preliminary contact via email, telephone calls, or text messaging. In addition, a link to an online version of the questionnaire, created using Monkey Survey©, was sent by text messaging or email to the representatives of the facilities. Reminders were sent via telephone calls or text messaging to maximize responses. Data collected included background information on the facility like name, address and head of the department, sub-specialties available, human resource for eye health and paediatric eye-care, and equipment details. An institute was assumed to be providing paediatric ophthalmology services only if it provided surgical paediatric eye care with availability of general anaesthesia facility. For such institutes, detailed information about paediatric ophthalmology services was obtained including diagnostic, out-patient, in-patient and surgical services. Duplicate data were removed promptly and incompletely filled forms were completed telephonically.

The second phase of the data collection started from July 2020 and was completed by December 2020. Representatives from NPCB&VI, Government of India was requested to issue a letter to all SPOs and DPOs informing them about the survey and soliciting their co-operation for the same. Starting from July 7, 2020, online orientation meetings were conducted with each state in which the respective SPO along with DPOs from all districts were invited. During these video-conferencing meetings, the questionnaire was explained in details and status of data collection was presented till the date of meeting. Opportunity was utilized to solve any queries regarding the questionnaire raised by the DPOs. Following the meet, email IDs and contact details of all DPOs was obtained from the SPO and district-wise database of eye institutes was emailed to each of them.

In each district, DPOs were telephonically requested to coordinate data collection and updating. DPOs also identified the other key informants / responsible persons from government / NGO or private section to collect information on human resource and infrastructure as per the questionnaire. For each state, Dr. Rajendra Prasad Centre for Ophthalmic Sciences recruited Coordinators from Community Ophthalmology section.
These coordinators were encouraged to use several sources of data including SPO/DPOs, professional networks (ophthalmologists and optometrists’ associations), medical colleges and eye care non-governmental organizations (NGOs). A separate What’s app group was formed in each state to resolve day-to-day queries. The daily reporting status was shared among the group members. Once the database was finalized in each district, efforts were made to obtain completed forms from each of the eye institute in that particular district.

QUALITY ASSURANCE:

In order to increase the validity of the data collected, triangulation method was used. The data obtained from each institute was emailed back to the head of the institute for confirmation and necessary rectification. This acknowledgement mail also ensured that the head of the department was aware of regarding the response received from their institute, so that any future rectification or updating can be done easily in the future.

DATA MANAGEMENT AND ANALYSIS

For consistency, all data was reviewed by a single researcher as it was received, to identify inconsistencies and likely reporting errors in the data requiring follow-up. Data that was received offline was entered directly into a Stata 15.0 (StataCorp, College Station, TX, USA) database and cross-checked for avoiding duplication. Stata 15.0 was used for all statistical analyses.

RESULTS

A total of 9440 eye institutes was identified after intensive online searched from the country. Out of them, 8790 (93.1%) institutes were contacted telephonically, and remaining institutes could not be contacted owing to lack of correct contact details. Out of the 8790 eye-care institutes in the country, complete responses were received from
7901 institutes (response rate 89.9%) and 2180 institutes (27.6%) reported to have paediatric eye care services. (Table 1, Figure 1)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>State</th>
<th>Number of eye-institutes (N=7901)</th>
<th>Paediatric eye institutes (N=2180)</th>
<th>Proportion of paediatric eye institute out of all eye institutes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Andhra Pradesh</td>
<td>397 (5.0)</td>
<td>68 (3.1)</td>
<td>17.1</td>
</tr>
<tr>
<td>2</td>
<td>Arunachal Pradesh</td>
<td>8 (0.1)</td>
<td>1 (0)</td>
<td>12.5</td>
</tr>
<tr>
<td>3</td>
<td>Assam</td>
<td>101 (1.3)</td>
<td>26 (1.2)</td>
<td>25.7</td>
</tr>
<tr>
<td>4</td>
<td>Bihar</td>
<td>248 (3.1)</td>
<td>57 (2.6)</td>
<td>22.9</td>
</tr>
<tr>
<td>5</td>
<td>Chattisgarh</td>
<td>103 (1.3)</td>
<td>29 (1.3)</td>
<td>28.2</td>
</tr>
<tr>
<td>6</td>
<td>Goa</td>
<td>62 (0.8)</td>
<td>7 (0.3)</td>
<td>11.3</td>
</tr>
<tr>
<td>7</td>
<td>Gujarat</td>
<td>648 (8.2)</td>
<td>206 (9.4)</td>
<td>31.8</td>
</tr>
<tr>
<td>8</td>
<td>Haryana</td>
<td>329 (4.2)</td>
<td>119 (5.5)</td>
<td>36.2</td>
</tr>
<tr>
<td>9</td>
<td>Himachal Pradesh</td>
<td>62 (0.8)</td>
<td>12 (0.6)</td>
<td>19.4</td>
</tr>
<tr>
<td>10</td>
<td>Jharkhand</td>
<td>183 (2.3)</td>
<td>51 (2.3)</td>
<td>27.9</td>
</tr>
<tr>
<td>11</td>
<td>Karnataka</td>
<td>504 (6.4)</td>
<td>127 (5.8)</td>
<td>25.2</td>
</tr>
<tr>
<td></td>
<td>State</td>
<td>Total Institutes</td>
<td>Paediatric Eye Institutes</td>
<td>Proportion</td>
</tr>
<tr>
<td>----</td>
<td>----------------</td>
<td>------------------</td>
<td>--------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>12</td>
<td>Kerala</td>
<td>219 (2.8)</td>
<td>40 (1.8)</td>
<td>18.3</td>
</tr>
<tr>
<td>13</td>
<td>Madhya Pradesh</td>
<td>242 (3.1)</td>
<td>67 (3.1)</td>
<td>27.7</td>
</tr>
<tr>
<td>14</td>
<td>Maharashtra</td>
<td>1360 (17.2)</td>
<td>492 (22.6)</td>
<td>36.2</td>
</tr>
<tr>
<td>15</td>
<td>Manipur</td>
<td>8 (0.1)</td>
<td>2 (0.1)</td>
<td>25.0</td>
</tr>
<tr>
<td>16</td>
<td>Meghalaya</td>
<td>14 (0.2)</td>
<td>3 (0.1)</td>
<td>21.4</td>
</tr>
<tr>
<td>17</td>
<td>Mizoram</td>
<td>11 (0.1)</td>
<td>7 (0.3)</td>
<td>63.6</td>
</tr>
<tr>
<td>18</td>
<td>Nagaland</td>
<td>9 (0.1)</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>19</td>
<td>Odisha</td>
<td>173 (2.2)</td>
<td>27 (1.2)</td>
<td>15.6</td>
</tr>
<tr>
<td>20</td>
<td>Punjab</td>
<td>324 (4.1)</td>
<td>118 (5.4)</td>
<td>36.4</td>
</tr>
<tr>
<td>21</td>
<td>Rajasthan</td>
<td>424 (5.4)</td>
<td>112 (5.1)</td>
<td>26.4</td>
</tr>
</tbody>
</table>

Table 1: State-wise proportion of eye-institutes and paediatric eye institutes

Figure 1: Proportion of eye institutes having paediatric oriented services out of total institutes.
INFRASTRUCTURE AND HR: STATES

The states contributing to the highest proportion of eye-institutes in the country include Maharashtra (17.2 %), Uttar Pradesh (9.1 %), Gujarat (8.2 %) & Karnataka (6.4 %). These four states along with Tamil Nadu, Andhra Pradesh, Telangana, Rajasthan & West Bengal constitute nearly two-thirds (67.7 %) of all eye-care institutes in the country. On the other hand, states like Madhya Pradesh (3.1 %), Bihar (3.1 %) & Odisha (2.2 %) have the lowest proportion of eye-care institutes in the country.

Out of the 7901 eye-care institutes in the country, 2180 (27.6%) of them were found to have paediatric oriented services.

The states contributing to the highest proportion of paediatric eye-institutes in the country include Maharashtra (22.6 %), Gujarat (9.4 %), Uttar Pradesh (8.9 %) & Karnataka (5.8 %). These four states along with Haryana, Punjab, Tamil Nadu & Rajasthan constitute nearly two-thirds (67.8 %) of all paediatric eye-care institutes in the country. On the other hand, states like Himachal Pradesh (0.6 %), Assam (1.2 %), Odisha (1.2 %) & Chattisgarh (1.3 %) have the least number of paediatric institutes in the country.

As far as the proportion of institutes having paediatric oriented services is concerned, the highest proportion was found in states like Punjab (36.4 %), Maharashtra (36.2 %) & Haryana (36.2 %). At the other end of the spectrum are states like Goa, Telangana, Sikkim, Arunachal Pradesh & Odisha where less one sixth of all eye institutes had paediatric oriented services.

Among the 9 union territories, the highest proportion of eye-institutes was found in Delhi (3.2 %), including the NCR (National Capital Region). The highest proportion of paediatric eye-institutes was also found in Delhi (5.0 %) followed by Chandigarh (0.5 %). UTs which did not have even one paediatric eye institute are Daman & Diu &
Lakshadweep. The proportion of total eye institutes having paediatric oriented services was highest in Chandigarh (47.6 %), closely followed by Delhi (43.8 %). (Table 2)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>State</th>
<th>Number of Eye-Institutes (N=7901)</th>
<th>Paediatric Eye-Institutes (N=2180)</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Andaman &amp; Nicobar Islands</td>
<td>1 (0)</td>
<td>1 (0)</td>
<td>100.0</td>
</tr>
<tr>
<td>2</td>
<td>Chandigarh</td>
<td>21 (0.3)</td>
<td>10 (0.5)</td>
<td>47.6</td>
</tr>
<tr>
<td>3</td>
<td>Daman &amp; Diu</td>
<td>1 (0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Dadra &amp; Nagar Haveli</td>
<td>4 (0.1)</td>
<td>1 (0)</td>
<td>25.0</td>
</tr>
<tr>
<td>5</td>
<td>Delhi</td>
<td>249 (3.2)</td>
<td>109 (5.0)</td>
<td>43.8</td>
</tr>
<tr>
<td>6</td>
<td>Jammu &amp; Kashmir</td>
<td>45 (0.6)</td>
<td>14 (0.6)</td>
<td>31.1</td>
</tr>
<tr>
<td>7</td>
<td>Lakshadweep</td>
<td>1 (0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Ladakh</td>
<td>2 (0)</td>
<td>1 (0)</td>
<td>50.0</td>
</tr>
<tr>
<td>9</td>
<td>Pondicherry</td>
<td>20 (0.3)</td>
<td>7 (0.3)</td>
<td>35.0</td>
</tr>
</tbody>
</table>

Table 2: Proportion of eye-institutes in Union Territories

INFRASTRUCTURES AND HR: NATIONAL

As far as ownership of eye-institutes is concerned, nearly 2/3rd of institutes (70.6 %) was in the private sector, followed by public sector (15.6 %) and NGO sectors (13.8 %). The number of optometrists per ophthalmologist at secondary / tertiary levels was 0.85. The ophthalmologist population ratio in the country was found to be 1: 65221 and the optometrist population ratio was 1:76530. Number of eye-beds per million population was 74. Proportion of eye institutes having 24 hours eye emergency was 40.5 %, while functional eye OT was reported by 87.0 % of institutes. Facility of eye bank (with tissue processing & storage) was reported by only 5.7 % of the institutes. Refractive eye surgery
was reported by 20.9% of institutes, whereas low vision services were reported by 28.3% of institutes. Most common sub-speciality services include cataract (91.5%), glaucoma (71.5%), squint (42.0%), oculoplasty (37.3%) and vitreo-retina (33.6%). Neuro-ophthalmology services were reported by only 25.4% of the institutes, whereas keratoplasty services were reported by only 14.4% of the institutes. (Table 3)

<table>
<thead>
<tr>
<th>Indicator Name</th>
<th>Description</th>
<th>Variables</th>
<th>N=7901</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ownership of Eye Services</td>
<td>Proportion of eye institutes owned by public, private or NGO sector</td>
<td>Public</td>
<td>1230</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Private</td>
<td>5580</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NGO</td>
<td>1091</td>
</tr>
<tr>
<td>Ophthalmologist: Optometrist Ratio</td>
<td>Number of optometrists per ophthalmologist at secondary / tertiary levels</td>
<td>Optometrists (17849)</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ophthalmologists (20944)</td>
<td></td>
</tr>
<tr>
<td>Ophthalmologist: Population Ratio</td>
<td>Number of ophthalmologists (both full time &amp; part time) per million population</td>
<td>Full time (15373)</td>
<td>15.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Part-time (5571)</td>
<td></td>
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<tr>
<td>Optometrist: Population Ratio</td>
<td>Number of optometrists per million population</td>
<td>Optometrists (17849)</td>
<td>13.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1:76530)</td>
<td></td>
</tr>
<tr>
<td>Eye Bed: Population Ratio</td>
<td>Number of eye-beds per million population</td>
<td>Eye-beds (100554)</td>
<td>74</td>
</tr>
</tbody>
</table>

Table 3: Indicators derived from the mapping of Human Resources & Infrastructure of Eye-care Services in India
<table>
<thead>
<tr>
<th>Types of Eye Services</th>
<th>Proportion of institutes with Eye Emergency, OT, Eye Banking and Low Vision Services</th>
<th>Emergency</th>
<th>OT</th>
<th>Eye Bank</th>
<th>Refractive Surgery</th>
<th>Low Vision Services</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3196</td>
<td>6877</td>
<td>449</td>
<td>1650</td>
<td>2233</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(40.5%)</td>
<td>(87.0%)</td>
<td>(5.7%)</td>
<td>(20.9%)</td>
<td>(28.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Types of Sub-specialties</th>
<th>Sub-speciality services in different areas of the country</th>
<th>Cataract</th>
<th>Glaucoma</th>
<th>Squint</th>
<th>Vitreo-retina</th>
<th>Keratoplasty</th>
<th>Oculoplasty</th>
<th>Neuro-ophthalmology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>7226</td>
<td>5653</td>
<td>3319</td>
<td>2653</td>
<td>1137</td>
<td>2950</td>
<td>2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(91.5%)</td>
<td>(71.5%)</td>
<td>(42.0%)</td>
<td>(33.6%)</td>
<td>(14.4%)</td>
<td>(37.3%)</td>
<td>(25.4%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eye OPD and Surgery: Population Ratio</th>
<th>Average Eye OPD and average surgeries per million population</th>
<th>Eye OPD/ 10 lac</th>
<th>Eye Surgery/ 10 lac</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>83,008</td>
<td>6178</td>
</tr>
</tbody>
</table>
The proportion of institutes having 24 hours eye emergency, functional eye OT, eye bank (with tissue processing facility), refractive eye surgery & low vision services was reported significantly higher in the private sector in comparison to the public sector and NGO sector. (Table 4). Similarly, the proportion of institutes having sub-specialities of cataract, glaucoma, squint, uvea & vitreo-retina, keratoplasty, oculoplasty & neuro-ophthalmology was reported significantly higher in the private sector in comparison to the NGO sector and public sector. (Table 5)

| Services                        | Government | NGO   | Private | Total  | p value |<| 0.0001 |
|---------------------------------|------------|-------|---------|--------|---------|<| 0.0001 |
| 24 Hours Eye Emergency          | 766 (23.9) | 538 (16.8) | 1892 (59.2) | 3196 |<| 0.0001 |
| Functional Eye OT               | 1096 (15.9) | 1047 (15.2) | 4734 (68.8) | 6877 |<| 0.0001 |
| Eye Bank                        | 125 (27.8) | 151 (33.6) | 173 (38.5) | 449 |<| 0.0001 |
| Refractive Eye Surgery          | 91 (5.5)   | 270 (16.4) | 1289 (78.1) | 1650 |<| 0.0001 |
| Low Vision Services             | 275 (12.3) | 466 (20.9) | 1492 (66.8) | 2233 |<| 0.0001 |
| Total                           | 1230       | 1091    | 5580    | 7901   |        |

Table 4: Ophthalmology services in different sectors among the surveyed eye-institutes

| Sub-specialities | Government | NGO   | Private | Total  | p value |<| 0.0001 |
|------------------|------------|-------|---------|--------|---------|<| 0.0001 |
| Cataract         | 1113 (15.4) | 1058 (14.6) | 5055 (69.9) | 7226 |<| 0.0001 |

123
<table>
<thead>
<tr>
<th>Glaucoma</th>
<th>724 (12.8)</th>
<th>828 (14.6)</th>
<th>4101 (72.5)</th>
<th>5653</th>
<th>&lt; 0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squint</td>
<td>298 (8.9)</td>
<td>532 (16.0)</td>
<td>2489 (74.9)</td>
<td>3319</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Uvea &amp; Vitreo-retina</td>
<td>185 (6.9)</td>
<td>444 (16.7)</td>
<td>2024 (76.3)</td>
<td>2653</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Keratoplasty</td>
<td>139 (11.3)</td>
<td>262 (23.0)</td>
<td>736 (64.7)</td>
<td>1137</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Oculoplasty</td>
<td>280 (9.5)</td>
<td>465 (15.8)</td>
<td>2205 (74.7)</td>
<td>2950</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Neuro-Ophthalmology</td>
<td>192 (9.6)</td>
<td>285 (14.2)</td>
<td>1530 (76.2)</td>
<td>2007</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Total</td>
<td>1230</td>
<td>1091</td>
<td>5580</td>
<td>7901</td>
<td></td>
</tr>
</tbody>
</table>

**Table 5: Ophthalmology sub-specialities in different sectors among the eye-institutes**

Out of the 2180 institutes reported of facilities of paediatric surgery under general anaesthesia, 71.3% were in the private sector, followed by NGO (17.2%) and public sectors (11.5%); and this difference was statistically significant. Paediatrician to handle cases were available in 1604 (73.5%) of the institutes & anaesthetists to handle paediatric cases were present in all institutes. Only 142 (6.5%) of the institutes were training institutes, providing formal training in the form of fellowship or senior residency in paediatric ophthalmology, and 45.8% of them were in private sector closely followed by the NGO sector (42.3%). Paediatric ophthalmology outpatient services (OPD) were
present in 1795 (82.3%) of the institutes & overnight admission facilities were present in 1206 (55.3%). (Table 6)

<table>
<thead>
<tr>
<th>Services</th>
<th>Government</th>
<th>NGO</th>
<th>Private</th>
<th>Total</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peadiatric eye Surgery (under GA)</td>
<td>251 (11.5)</td>
<td>375 (17.2)</td>
<td>1554 (71.3)</td>
<td>2180</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Paediatrician to handle cases</td>
<td>235 (14.6)</td>
<td>289 (18.01)</td>
<td>1080 (67.3)</td>
<td>1604</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Training Institute (fellowship or SR)</td>
<td>17 (11.9)</td>
<td>60 (42.3)</td>
<td>65 (45.8)</td>
<td>142</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Paediatric OPD (&lt;18years)</td>
<td>192 (10.7)</td>
<td>325 (18.1)</td>
<td>1278 (71.2)</td>
<td>1795</td>
<td>0.0047</td>
</tr>
<tr>
<td>Overnight admission facilities (&lt;18years)</td>
<td>200 (16.6)</td>
<td>278 (23.1)</td>
<td>728 (60.4)</td>
<td>1206</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total</td>
<td>251</td>
<td>375</td>
<td>1554</td>
<td>2180</td>
<td></td>
</tr>
</tbody>
</table>

Table 6: Paediatric Ophthalmology services in different sectors among the eye-institutes

The availability of paediatric equipment was also highest in the private sector, followed by NGO sector & public sector. (Table 7)

<table>
<thead>
<tr>
<th>Equipment</th>
<th>Government</th>
<th>NGO</th>
<th>Private</th>
<th>Total</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-verbal Teller’s/Cardiff cards</td>
<td>95 (7.1)</td>
<td>259 (19.4)</td>
<td>979 (73.4)</td>
<td>1333</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Trial Sets</td>
<td>223 (10.8)</td>
<td>359 (17.3)</td>
<td>1490 (71.9)</td>
<td>2072</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prisms for Squint Assessment</td>
<td>182 (10.1)</td>
<td>319 (17.8)</td>
<td>1296 (72.1)</td>
<td>1797</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Retinoscope1</td>
<td>240 (11.3)</td>
<td>371 (17.4)</td>
<td>1518 (71.3)</td>
<td>2129</td>
<td>0.0267</td>
</tr>
<tr>
<td>Equipment</td>
<td>Mean (S.D.)</td>
<td>Median (Median)</td>
<td>Min (Max)</td>
<td>P-value</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>-------------</td>
<td>-----------------</td>
<td>-----------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Handheld Tonometer-Schiotz etc</td>
<td>194 (11.2)</td>
<td>330 (18.9)</td>
<td>1213 (69.8)</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Other Tonometer (NCT, Goldman)</td>
<td>197 (10.1)</td>
<td>338 (17.5)</td>
<td>1399 (72.3)</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Indirect Ophthalmoscope</td>
<td>236 (11.1)</td>
<td>369 (17.4)</td>
<td>1516 (71.5)</td>
<td>0.0021</td>
<td></td>
</tr>
<tr>
<td>RetCam/Paediatric Fundus Cam</td>
<td>46 (7.3)</td>
<td>133 (21.1)</td>
<td>450 (71.5)</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>ROP laser</td>
<td>96 (8.9)</td>
<td>205 (19.1)</td>
<td>770 (71.9)</td>
<td>0.0002</td>
<td></td>
</tr>
<tr>
<td>A scan Ultrasound</td>
<td>233 (11.1)</td>
<td>361 (17.2)</td>
<td>1499 (71.6)</td>
<td>0.0233</td>
<td></td>
</tr>
<tr>
<td>Keratometer</td>
<td>238 (11.5)</td>
<td>366 (17.6)</td>
<td>1472 (70.9)</td>
<td>0.0606</td>
<td></td>
</tr>
<tr>
<td>Operating Microscope</td>
<td>247 (11.5)</td>
<td>372 (17.3)</td>
<td>1532 (71.2)</td>
<td>0.6265</td>
<td></td>
</tr>
<tr>
<td>Phaco Machine</td>
<td>209 (10.1)</td>
<td>361 (17.5)</td>
<td>1495 (72.4)</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Vitrectomy Machine</td>
<td>121 (7.4)</td>
<td>293 (18.0)</td>
<td>1213 (74.5)</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>251</td>
<td>375</td>
<td>1554</td>
<td>2180</td>
<td></td>
</tr>
</tbody>
</table>

**Table 7: Paediatric Ophthalmology equipment available in different sectors**

As per the current survey, there are around 16 paediatric eye-care institutes per 10 million population in the country, and the number of paediatric ophthalmologist (having received formal training or fellowship in paediatric ophthalmology) per 10 million was 8. The
The average eye OPD per million population was 83,008 for general ophthalmology, which includes 43,760 of paediatric (up to 18 years) patients. Similarly, the average eye surgery per million population was 6,178 for general ophthalmology, which includes 112 of paediatric (up to 18 years) patients. Out of 100 paediatric eye institutes, average of 6-7 provide formal training (fellowship or senior residency) in paediatric ophthalmology.

(Table 8)

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Description</th>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paediatric Eye Institute: Population Ratio</td>
<td>Number of paediatric eye institutes per 10 million population</td>
<td>Paediatric eye Institutes (2180)</td>
<td>16</td>
</tr>
<tr>
<td>Ophthalmologist: Population Ratio</td>
<td>Number of paediatric ophthalmologists per 10 million population</td>
<td>Paediatric Ophthalmologist (1087)</td>
<td>8</td>
</tr>
<tr>
<td>Paediatric Eye OPD and paediatric Surgery: Population Ratio</td>
<td>Average Paediatric Eye OPD and average surgeries per million population</td>
<td>OPD/10 lac</td>
<td>4376</td>
</tr>
<tr>
<td>Proportion of training institutes</td>
<td>Proportion of paediatric institutes in the country providing training in paediatric ophthalmology</td>
<td>Training Institutes (142)</td>
<td>6.5</td>
</tr>
<tr>
<td>Paediatric Eye Bed: Population Ratio</td>
<td>Number of paediatric eye-beds per million population</td>
<td>Total Paediatric Eye beds (3436)</td>
<td>3</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-----------------------------------------------------</td>
<td>---------------------------------</td>
<td>---</td>
</tr>
<tr>
<td>Proportion of Sub-speciality surgeries</td>
<td>Proportion of surgical procedures in various subspecialties of out of total paediatric ophthalmology surgeries</td>
<td>Cataract</td>
<td>34.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glaucoma</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Squint</td>
<td>17.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ROP</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Keratoplasty</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oculoplasty/Oncology</td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Others</td>
<td>29.1</td>
</tr>
</tbody>
</table>

Table 8: Indicators in HR and Infrastructure for paediatric eye care in India

On an average, there are 7.4 eye beds per million population, out of which only 3 beds are dedicated to paediatric patients. The proportion of total eye operations that were performed on paediatric patients was 1.8 %. Among the paediatric surgeries, the highest proportion was for cataract (34.1 %), followed by other adnexal operations (29.1 %) and squint (17.7 %). The proportion of glaucoma surgeries was 3.9 %, oculoplasty/oncology was 9.3 % and keratoplasty 1.6 %. (Table 8) Out of total paediatric OPD, proportion of ROP screening was 5.3 %. Out of all the children screened, LASER was performed on 8.3 % of
the patients. The proportion of ROP surgery among all paediatric surgeries was 4.3 %. (Table 9)

<table>
<thead>
<tr>
<th>Indicator for ROP</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROP patients screened (out of total Paediatric OPD)</td>
<td>311729 (5.3)</td>
</tr>
<tr>
<td>ROP LASER performed (out of children screened for ROP)</td>
<td>25962 (8.3)</td>
</tr>
<tr>
<td>ROP Surgery (out of children screened for ROP)</td>
<td>6449 (4.3)</td>
</tr>
</tbody>
</table>

Table 9: Status of Retinopathy of Prematurity (ROP) services in the Paediatric Eye Institutes

A list of 14 equipment was used in the survey to assess the infrastructure for providing paediatric eye care; the instruments were divided into those required for OPD & those required for surgery. Proportion of paediatric eye institutes having functional retinoscope was 97.6 % indirect ophthalmoscope 97.3 %, trial sets 95.0 %, prisms for squint assessment 82.4 %, handheld tonometer 79.7 % and other tonometer 88.7 %. Pre-verbal vision test (Teller’s/Cardiff VA Card) was available with only 61.1 % of the eye institutes, whereas RetCam/Paediatric fundus camera was available with only 28.9 % of institutes. (Table 10)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Equipment for Paediatric Refraction &amp; OPD</th>
<th>Number (%) (N=2180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pre-verbal vision test (Teller’s/Cardiff VA Card)</td>
<td>1333 (61.1%)</td>
</tr>
<tr>
<td>2</td>
<td>Trial sets</td>
<td>2072 (95.0%)</td>
</tr>
<tr>
<td>3</td>
<td>Prisms for Squint Assessment</td>
<td>1797 (82.4%)</td>
</tr>
<tr>
<td>4</td>
<td>Retinoscope</td>
<td>2129 (97.6%)</td>
</tr>
<tr>
<td>5</td>
<td>Handheld Tonometer-Schiotz/Perkins/Tonopen</td>
<td>1737 (79.7%)</td>
</tr>
<tr>
<td>6</td>
<td>Other Tonometer (NCT, Goldmann etc)</td>
<td>1934 (88.7%)</td>
</tr>
<tr>
<td>7</td>
<td>Indirect ophthalmoscope</td>
<td>2121 (97.3%)</td>
</tr>
<tr>
<td>8</td>
<td>RetCam/Paediatric fundus camera</td>
<td>629 (28.9%)</td>
</tr>
</tbody>
</table>
Table 10: Proportion of paediatric institutes in the country having requisite equipment for Paediatric refraction and surgery

<table>
<thead>
<tr>
<th>Equipment for Paediatric Surgery</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ROP laser (Laser Indirect Ophthalmoscopy)</td>
<td>1071 (49.1%)</td>
</tr>
<tr>
<td>2 A-scan ultrasound</td>
<td>2093 (96.0%)</td>
</tr>
<tr>
<td>3 Keratometer</td>
<td>2076 (95.2%)</td>
</tr>
<tr>
<td>4 Operating Microscope</td>
<td>2151 (98.6%)</td>
</tr>
<tr>
<td>5 Phaco Machine</td>
<td>2065 (94.7%)</td>
</tr>
<tr>
<td>6 Vitrectomy Machine</td>
<td>1627 (74.6%)</td>
</tr>
</tbody>
</table>

Similarly, proportion of paediatric eye institutes having functional operating microscope was 98.6 %, A-scan ultrasound 96.0 %, keratometer 95.2 % and phaco machine 94.7 %. Vitrectomy machine was available with 74.6 % of institutes, whereas ROP laser was available with only 49.1 % of institutes. (Table 10)

DISCUSSION

A child becomes bilaterally blind every minute, primarily within developing nations. Such children need to be addressed to achieve the goal of Vision 2020- The Right to Sight. The number of optometrists per ophthalmologist at secondary / tertiary levels in the current study was 0.85 in the current study. Ideally the ratio of paramedics should be 3 to 4 per ophthalmologist. Although the target year 2020 has already arrived, there is still a long way to go to achieve adequate number of ophthalmic paramedics in the country. The ophthalmologist population ratio in the country was found to be 1: 65221. Again, the target for ophthalmologists was to achieve a ratio of 1:50000 with at least 25 000 trained ophthalmologists by 2020. The number of ophthalmologists in the current survey was 20944. Even if we add 10 % to this number due to non-response by institutes, it still falls short of the 25000 required to achieve in the country by 2020. One encouraging finding of
the survey was 8 paediatric ophthalmologists per 10 million population which is a much more optimistic figure than the minimum requirement of 1 per 10 million.

There has been no formal training for paediatric ophthalmology till recently, although paediatric ophthalmology departments are now being set up in tertiary care eye hospitals. Such departments do not cater only to children but provide services across all age groups. Only recently have institutions like Aravind Eye Care System, Sankara Netralaya and L.V. Prasad Eye Institute, which have been labelled as paediatric ophthalmology learning and training centres, have formalized fellowship programs in paediatric ophthalmology. More ophthalmologists are now opting for paediatric ophthalmology fellowship training.

Though paediatric ophthalmology is now developing as a distinct subspecialty in India, the clinical load may not warrant a situation in most hospitals of specialty ophthalmologists working only in paediatric ophthalmology. To attract ophthalmologists to take up paediatric ophthalmology, it would be necessary to allow them to also attend to ophthalmic problems in other age groups to generate adequate professionally satisfying workloads.[12]

Though a significant number of hospitals in the country have either specialty trained or oriented ophthalmologists, they are usually not supported by a trained paediatric team, as was observed in the present study. The subspecialty needs a team approach to be successful and identifying modalities of training a composite team of ophthalmologists, optometrists, nurses, anaesthesiologist and counsellors needs to be addressed. The WHO also strongly recommends the team approach.[10]

The present study was one of its kind in the Indian subcontinent to collect information on the status of paediatric eye care services. The WHO suggests that there should be one paediatric ophthalmology service centre for every 10 million population, where at least
one specialty trained or oriented ophthalmologist should be available. There were 2180 such centres for a population of 1.3 billion, translating to 8 paediatric ophthalmology service units per 10 million population. Many of these hospitals do not have a full complement of diagnostic and surgical equipment, infrastructure and supportive human resources to provide vibrant paediatric ophthalmology services. The available centres are also not homogenously distributed across the country. Better ratios were observed in the southern and western part of India as against thin distribution of services in the North and East. Paediatric eye care services need further strengthening via investment of time and money, and a professional and political commitment is required to support the establishment of need-based paediatric centres.

BIBLIOGRAPHY


10. World Health Organization (WHO). A five-year project for the prevention of childhood blindness. 2002;


Phase ½ A Study Of Intravitreal Optogenetics Gene Therapy For Vision Restoration In Advanced Retinitis Pigmentosa

Dr. Santosh Mahapatra

ABSTRACT

PURPOSE:

Optogenetics therapy offers the potential for vision restoration in patients with photoreceptor degeneration. Through the delivery of opsin encoding genes, residual retinal neurons take on the photosensitizing function of the photoreceptors. Such an approach focuses on disease phenotype versus a specific genotype deficit, therefore applicable to a wide patient population. Existing optogenetic tools utilize opsins that do not generate adequate electrical current in ambient light requiring an external device for stimulation. Hence, this study aims at targeting bipolar cells modifying them to be ambient light activable photoreceptor cell by intravitreal introduction of multi characteristic opsin carried by Adeno Associated Virus 2 (AAV2) vector.

METHOD:

Multi-Characteristic Opsin (MCO) is an engineered opsin that can be used to photosensitize higher order retinal cells with the potential for greater spatial resolution at ambient light
levels, thereby avoiding the need for an external amplifying device and associated phototoxicity. AAV2 was used to deliver MCO1 in advanced retinitis pigmentosa subjects. Subjects received prophylactic oral steroids prior to a single intravitreal injection of AAV2-MCO1 (vMCO-l). Safety and exploratory efficacy of intravitreal vMCO-l dose escalation were evaluated to identify a safe dose.

RESULT:

vMCO-l was well tolerated with no reported serious adverse events at end of the study at 16 weeks. Ocular adverse events were limited to inflammation and rise in intraocular pressure that were controlled with topical medications. Furthermore, exploratory endpoints demonstrated improvement in vision and visual function in retinitis pigmentosa subjects following a single dose.

CONCLUSION:

vMCO-l is well tolerated with no serious adverse events. Higher dose vMCO-l appears to improve visual acuity and visual function at 16 weeks compared to baseline measurements and demonstrates tremendous promise in restoring vision for retinitis pigmentosa patients.

INTRODUCTION:

In retinal degenerative diseases such as Retinitis Pigmentosa (RP), Stargardt’s disease, Leber’s congenital amaurosis (LCA) and Cone-rod Dystrophy, the photoreceptors that are responsible for conversion of light into electro-chemical signals, are degenerated. This prevents the generation of photo-induced signals in retina, breaking the vision-sensory related cascade of events within the visual system. Loss of photoreceptor cells and/or loss of photoreceptor cell function are the primary causes of reduced light sensitivity and blindness in advanced stage of retinal dystrophy.
Retinitis Pigmentosa (RP) refers to disorders characterized by degeneration of photoreceptors in the eye, which hinders visual ability by non-functional neuronal activation, and transmission of signals to the visual cortex \(^{(1,5)}\). The prevalence of RP is approximately 100,000 patients in the US, out of which ~50,000 patients have advanced retinal dystrophy. Assuming the report of 1 in every 3000 people has RP, India has RP patient population > 460,000. RP is most often inherited as an autosomal recessive trait with large number of cases having this form of inheritance \(^{(3,6,7)}\). Further, the degree of visual loss increases with ageing \(^{(8)}\) and this is a major concern for our demographic changes towards elderly population. In some people, RP advances so slowly that vision loss does not occur for a long time. In others, the disease progresses faster and may lead to a loss of vision in one or both eyes. Most of the current clinical treatments are primarily focused on slowing down the progression of the disease \(^{(9)}\), as there is neither a cure that can stop the degeneration \(^{(10)}\) nor a therapy, other than retinal prostheses, that can restore vision lost due to the degeneration \(^{(11)}\). Partial restoration of vision involves invasive surgical procedure for retinal implants \(^{(12)}\). Two different types of retinal Implants are being developed: subretinal and epiretinal implants \(^{(13)}\). The subretinal implants are positioned in the area of the retina where the photoreceptor cells reside, between the pigmented epithelium and the bipolar cells \(^{(14)}\). These retinal prostheses have been successful in generating visual perception in blind subjects \(^{(15-17)}\). The disadvantages of using such subretinal implants include (i) chronic damage of the implanted electrodes, and (ii) insufficient current produced by microphotodiode from the ambient light to stimulate adjacent neurons \(^{(18,19)}\). The epiretinal implants are placed in the area of the retinal ganglion cells (RGCs) and the device functions by stimulating the RGCs in response to input obtained from a camera that is placed outside of the eye or within an intraocular lens \(^{(19,20)}\). The disadvantages of epiretinal implants include (i) cellular outgrowth due to surgical implantation, and (ii) disordered stimulation pattern resulting from the electrical stimulation of both the axons and cell bodies of the RGCs \(^{(19)}\). Besides being invasive in nature, these methods for restoration of vision in blind patients are based on non-specific
cellular activation and have low spatial resolution due to low number of electrodes (higher number or density of electrodes requires more power, leading to damage of neural tissue by heat), and hence able to improve vision with low spatial resolution.

In advanced stages of retinal degenerative diseases such as RP, the photoreceptors that are responsible for conversion of light into electro-chemical signals are degenerated. This prevents the generation of photo-induced signals in retina, breaking the vision-sensory related cascade of events within the visual system. There is no cure for these diseases, especially in the advanced stages. Since higher order neurons are still intact in degenerated retina, several stimulation methods target the higher order neurons, e.g. Bipolar cells and retinal Ganglion cells, which carry the visual information to the visual cortex. While direct electrical stimulation approaches require mechanical contact of electrodes to the retinal cells, indirect stimulation approaches such as optogenetic stimulation does not necessitate such physical contact. Thus, the indirect methods provide clear advantage of being non-intrusive. In addition, cellular specificity can be achieved while using optogenetic stimulation. Optogenetic method has been employed for vision restoration in blind mice model either by non-specific stimulation of retina \(^{21}\) or in a promoter-specific manner including Thyl for RGCs \(^{22-26}\), mGluR6 targeting ON bipolar cells \(^{27,28}\).

The earlier approaches for restoration of vision by optogenetic stimulation of retinal cells use opsins such as ChR2 \(^{21}\) and others, which requires light intensities order of magnitude higher than ambient lighting conditions. Therefore, clinical success of such opsin molecules in ambient environment for vision restoration is not yet achieved. Further, use of external light source or device (e.g. LED array \(^{29}\)) to activate such opsins can substantially damage the retinal cells in long-term usage. Therefore, effective optogenetic vision restoration at ambient light level has not been shown yet. By photosensitizing higher order retinal neurons (e.g. bipolar cells) with ambient light-sensitive ion-channel proteins (MCO-010), delivered via safe viral vectors, we aim to
restore light sensitivity of retina and thus vision lost due to degenerative diseases.

**METHODS:**

The study was conducted in accordance with ICH and GCP guidelines and approval from institutional ethical committee was obtained before commencement of the study. Informed consent was taken from all study subjects in accordance with guidelines of Declaration of Helsinki.

The study included all the cases presenting to a tertiary care eye hospital in Eastern India with advanced RP after preliminary screening to fit into to the inclusion and exclusion criteria as noted below

**INCLUSION CRITERIA**

1. Age > 18 years
2. Ability to comply with testing and all protocol tests.
3. Diagnosis of advanced RP based on
   a. Clinical diagnosis and fundus photography
   b. Prior documented (if any) retinal electrophysiological evidence of rod-cone photoreceptor degeneration
4. Snellen's visual acuity equivalent LP/NLP in worse (study) eye
5. Visual acuity in the non-study eye of no-better-than finger counting
6. Presence of retinal bipolar cells and retinal nerve fiber layer on OCT testing
7. Women of childbearing potential must have a negative pregnancy test at the
screening

9. Males must use effective forms of contraception during the study period

EXCLUSION CRITERIA

1. Participation in a clinical study (ocular or non-ocular) with an investigational drug, agent or therapy in the past six months.

2. Concurrent participation in another interventional clinical ocular study.

3. Prior participation in any gene or stem cell therapy (ocular or non-ocular).

4. Pre-existing eye conditions that would preclude the planned treatment (i.e. injection) or interfere with the interpretation of study endpoints or surgical complications (example would include, but not limited to, glaucoma, diseases affecting the optic nerve causing significant visual field loss, active uveitis, corneal or lenticular opacities).

5. Complicating systemic diseases or clinically significant abnormal baseline values.

6. Subjects with any immunological response dysfunction, for example, immuno-compromising diseases or use of immunosuppressive medications, among others. Subjects who are positive for hepatitis B, C, and HIV will be excluded.

7. Cataract surgery, intraocular and/or peri-ocular injection in the study eye within the prior three months.

8. Opacity of lens > 3+ due to cataract or significant media opacities hindering visualization of fundus or performance of OCT in the study eye.

9. Known sensitivity to any component of the study agent or medications planned for use in the peri-operative period.

10. Current pregnancy or breastfeeding.
11. Subjects will be excluded if immunological studies show presence of neutralizing antibodies to AAV2 above 1:1000.

12. Any other condition that would not allow the potential subject to complete follow-up examinations during the course of the study and, in the opinion of the investigator, makes the potential subject unsuitable for the study.

13. Presence of narrow iridocorneal angles contraindicating pupillary dilation.

14. Presence of any macular pathology causing decrease in vision or retinal detachment involving macula.

15. Active ocular inflammation or recurrent history of idiopathic or autoimmune associated uveitis.

The investigational product is AAV2 carrying Multi Characteristic Opsin (MCO1) which have obtained orphan drug status by USFDA. The drug needs to be kept between minus 70 to minus 80 degree centigrade throughout the transportation & storage.

This phase I/IIa clinical study is an open label-dose exploration and expansion in which 3 subjects received low dose (2.5 E11 vg/eye) uniocular intravitreal injection of vMCO-I (in the worst eye). Upon confirming the safety of the low dose, 3 more subjects received the high dose (5.0 E11 vg/eye). Once it was confirmed that the high dose subjects showed safety and tolerability, 5 more subjects received the high dose of 5E11 vg/eye through intravitreal administration. The subjects were regularly monitored and followed up according to the schedule mentioned on day 1, 2nd, 4th, 8th, 12th, 16th & 52nd week. (Fig. – 1)

The objectives of this Phase I/IIa clinical study is to:
a) Evaluate the safety and tolerability of the intravitreal administration of adeno-associated virus, serotype 2 (AAV2) carrying ambient light activatable Multi Characteristic Opsin (vMCO-I) in patients with advanced RP.

b) To define the safety (Phase I) and confirm highest tolerated dose (Phase IIa) and recommend Phase IIb dose

Data was collected on a standardised form, which included age, sex, address, presenting vision, ophthalmic examination, investigations, number of follow ups, sequelae, complications and final visual outcome. A detailed history was taken. All subjects underwent comprehensive ophthalmologic examination. Complete external examination was done by slit lamp biomicroscopy, intraocular pressure (IOP) was measured by using rebound tonometer (I-care). Fundus was evaluated using 90 D Volk lens and by indirect ophthalmoscopy with 20 D lens. Screening for pregancy, HIV, HBSAg, fasting blood sugar (FBS), postprandial blood sugar (PPBS), complete blood count (CBC), lipid profile and renal profile were done for every patient.

Under aseptic conditions, patients underwent intravitreal injection of vMCO1 in the operating room under topical anaesthesia using 30 G needle in a micro titrated syringe. Subjects were on an oral regimen of systemic corticosteroids beginning three days before the administration of vMCO-I (Day-3). The initial dose was 1 mg/kg/day prednisone for seven days, with a maximum prescribed dose of 40 mg/day, regardless of the weight of the subject; this was followed by 0.5 mg/kg/day prednisone for an additional five days, with a maximum prescribed dose of 20 mg/day, regardless of the weight of the subject. Subjects were on systemic corticosteroids for a minimum of 12 days up to a maximum of 30 days, depending on the post-injection inflammation.

Subjects with mild inflammation received topical steroids or periocular/sub-Tenon/intravitreal triamcinolone acetonide at the discretion of the investigator. Some subjects were treated for increase in intraocular pressure with IOP lowering medicines.
Subjects underwent recording of Adverse Events as reported by participant or observed by investigator. Recorded concurrent medications, Recorded vital signs, weight, Physical examination, Functional assessment of vision by Electro Retinogram (ERG), Visual performance status by Low Vision Multi parametric test (LVMPT), Full-field light sensitivity threshold, Fundus photography, Visually-guided behavioral assays, Performed OCT imaging, record results, Visual function questionnaire, Best-corrected visual acuity (Freiburg ACT), Humphrey Visual Field in each visit. Blood drawn (for Neutralizing Antibody assay and Complete Blood Count on 4th week and for genotyping on 8th week.

All data were analysed using SPSS software version 24.42 (IBM SPSS Statistics 24.42, www.spss.co.in, India) for windows. Statistical analysis was done and significance of correlation for each parameter was calculated using Chi-square test and descriptive statistics. Percentages and frequencies were calculated for demographic variables as well as clinical parameters. Tables and graph was used to present the results.

RESULTS:

The totality of data from clinical development program demonstrates that vMCO-I has positive safety profile at the dose of 5.0E11 vg / eye. The study also demonstrated the evidence of efficacy at the end of 16 weeks after intravitreal injection. Improvements in both visual function and functional vision was reported as early as 4 weeks which further improved through 16 weeks. There was no major AEs reported upon administration of vMCO-I. An interesting observation that was visible during this study was the presence of MCO-010 reporter (mCherry) in the contralateral eyes of some patients which led to improvement in the contralateral eye too. The logMAR acuity value of injected eyes in the high-dose group showed improvement of 0.68 as compared to 0.1 logMAR in low-dose group 16 weeks after injection. The mean improvement in the logMAR acuity in high-dose contralateral eyes was found to be 0.34 logMAR at 16 weeks as compared to improvement of 0.68 logMAR acuity in the injected eyes. Dose-dependent improvement
in FST-value was observed in both injected and contralateral eyes. An increased visual field index in 30-2 Humphrey visual assessment was observed in both injected and contralateral eyes for few patients.

Longitudinal measurement using LVMPT showed that the intensity threshold to detect different static shapes correctly reduced after vMCO-010 injection. Further, at the threshold intensity level (22 Lux), the shape (circle, triangle and square) determination accuracy increased from ~50% at baseline to 100% at >8 weeks for both injected and contralateral eyes. Similar test for determining the Size threshold for detecting different shapes reduced to half after vMCO-010 injection implying halving of visual angle. In addition, longitudinal measurement using LVMPT showed that the accuracy (%) in detection of direction of Optical Flow increased from ~40% at baseline to ~100% at >8 weeks for both vMCO-010 injected and contralateral eyes. Furthermore, the upper speed threshold (to accurately detect direction of optical flow) increased significantly (mean value more than doubled) 8 weeks after vMCO-010 injection.

For both Y- and A-Mobility tests, the mean latency and standard error around mean to find lighted panel is decreased significantly after vMCO-10 injection as compared to the baseline. Light-intensity dependent improvement was observed in A-Mobility assay with the mean latency and standard error around mean for 1 lux assay was found to be lower than that at 0.5 lux at >4 weeks after vMCO-010 injection. The Mobility scores in both Y- and A-Mobility tests improved after vMCO-010 injection and this improvement was observed bilaterally. Overall, all the subjects in all trials made less errors and performed the tasks faster after vMCO-010 injection irrespective of presence (A-maze) or absence (Y-maze) of obstacles, position of the lighted LED panel (left or right), starting positions (middle or off-centered), or intensity levels (0.5, 1 lux) of the lighted LED panel.

The overall composite score and the three subscales (near activities, distance activities, and vision-specific dependency) showed significant improvement at 4, 8 and 16 weeks
after injection. The increasing trend of the scores was associated with the increase in the measured visual acuity and other visual functions, namely light stimulation threshold, visual field, shape and direction recognition ability, visually guided mobility etc. Vision-specific dependency subscale score increased the most among the other subscale scores. This increased subscale score correlated with anecdotes from the subjects and their family members.

A comprehensive ophthalmic assessment with dilated fundus examination was performed to grade the magnitude of the inflammation by compartment and severity, according to the SUN criteria for anterior chamber (AC) cell and flare (30), and the NEI grading scheme for vitreous haze (30,31).
Mild to moderate ocular inflammation and increase in IOP in some subjects were observed and were treated with topical steroid and/or IOP-lowering drops (Fig. 2). S-003 (low dose) and S-006 (high dose) had moderate increase in IOP level after injection. Few other subjects had mild increase in IOP, which was controlled via application of topical steroid / IOP-lowering drug without requiring surgery. At 16 weeks, the average IOP level maintained similar to normal values. To evaluate if elevated IOP was related to vMCO-010 injection related intraocular inflammation, ocular adverse events were evaluated by slit lamp and indirect ophthalmoscopy.

No subject had an ocular inflammation score greater than 2 at any timepoint during the study. At 2 weeks after injection, 1 subject (S-006) had AC/Vitreous AE grade 2 and 2 subjects (S-010, 011) had AC/Vitreous AE Grade of 1. At 4 weeks, 2 subjects (S-005, 006) had AC/Vitreous AE grade 2/1 and 1 subject (S-011) had AC/Vitreous AE Grade of 1. At 8 weeks of injection, only 1 subject (S-005) had AE Grade of 1 in AC/Vitreous. 5 subjects (S-001, 002, 009, 010, 011) had AE score Grade of 1 in AC/Vitreous at 12 weeks after injection and 1 subject (S-006) has AC/Vitreous AE grade 1/2. At 16 weeks, 1 subject (S-006) had vitreous Haze AE grade 2; 5 subjects (S-001, 003, 004, 005, 008) had AC/Vitreous AE Grade of 1. An ocular AE (Keratic precipitate) in 1 subject (S-005) leading to
corneal endothelial deposit could not be confirmed to be related to intravitreal injection. Fig. 3 shows the longitudinal assessment of Anterior Chamber Cell and Anterior Chamber Flare in the injected and contralateral eyes. In Fig. 4, we show longitudinal assessment of Vitreous Cell and Vitreous haze in injected and contralateral eye and Fig. 5 shows the details of the intervention for ocular inflammation in subjects having AE score > 0.
Fig. 4. Longitudinal assessment of Ocular inflammation in injected and contralateral eye. 

Fig. 5. Details of Intervention for Ocular inflammation in subjects having AE score.
Retinal thinning is known to occur in RP due to progressive nature of the degeneration. To monitor the rate of retinal thinning and to evaluate retinal thinning (if any) due to vMCO-I injection, OCT imaging of retina was carried out in a longitudinal manner. In Fig. 6, we have shown OCT images of injected eye at Baseline and 16 weeks after injection in 2 low dose and 2 high dose subjects having ocular inflammation. Longitudinal assessments of retinal thickness in these subjects (Fig. 6) show no dependence on administered dose or change in IOP.

Longitudinal monitoring of retinal thickness in injected and contralateral eyes was carried out by OCT imaging and quantified (Fig. 7). Measured average retinal thickness did not change after vMCO-010 injection. No significant change in retina thickness was observed at 16 weeks with respect to baseline.
The vMCO-010 safety profile remains satisfactory and MCO-010 was well-tolerated 16 weeks after intravitreal injection. No serious adverse events observed in vMCO-010 injected eyes or contralateral eyes and all dosed subjects continue active participation. Mild to moderate ocular inflammation and increase in IOP in some subjects was treated with topical steroid and/or IOP-lowering drops. There was no itching, pain or redness of eye reported by the subjects. Furthermore, no significant change in retina thickness was observed at 16 weeks with respect to baseline as measured by OCT. The analysis of AAV2 neutralizing antibody 4 weeks after injection shows no detectable increase suggesting no systemic immune response.

**DISCUSSION**

MCO-010 is an ambient light-activatable ion channel protein, which opens up when exposed to light allowing flow of cations into the cell. Our in-vivo animal results show significant photo-induced inward current upon activation of MCO-010 expressing cells by low intensity of light. vMCO-I is MCO-010 carried by adeno-associated virus serotype 2 (AAV2), which is naturally replication deficient, requiring co-infection with helper viruses to replicate. The wild-type virus consists of a single-stranded DNA genome encapsulated in a protein coat. The genome consists of three elements: the rep gene, the cap gene, and the inverted terminal repeats (ITRs). The rep gene codes for proteins
involved in DNA replication, and the cap gene, which, through a differential splicing mechanism, encodes three amino-terminal variant virus proteins, VP1, VP2 and VP3, that make up the coat of the virus.

In order to achieve optogenetic stimulation of retinal neurons, the retinal cells especially the ON bipolar cells are generally transfected by a vMCO-I (administered intravitreally) to express multi-characteristic opsin (light-sensitive molecular ion-channel), which gets activated, thus depolarizing the opsin-expressing retinal bipolar cells when illuminated by ambient light in broad visible spectrum (characteristics of the multi-characteristic opsin). The photosensitized bipolar cells have shown to drive retinal circuitry functions, activate cortical circuits, and mediate visually guided behaviors.

The doses and injection volume have been calculated by allometric scaling from preclinical animal studies. Vitreous humor volume was the scaling factor across species. In general, scaling of the vitreous volume from mice to humans is 1:1000. In our preclinical studies, we have conducted biodistribution analysis in non-targeted tissues (using quantitative PCR) and toxicity studies (i.e. pro-inflammatory cytokine quantification using ELISA, apoptotic biomarker expression in retina) in rd10 mice after vMCO-I injection. We have used intravitreal dose up to 1.0 E10 vg/eye in mouse and found it to be safe as evaluated by OCT for ocular structures, ELISA for inflammatory cytokines, QPCR for biodistribution and immunostaining for determining immune cell response. The GLP toxicity studies (Ophthalmic examinations, ERG, IOP, Body weight, Tear test, ELISA, Clinical Pathology, Histopathology, Biodistribution and immunohistochemistry) on wild type dogs conducted by CRO (Contract Research Organization) did not show limiting toxicity for dose up to 0.64 E12 vg/eye. Therefore, the expected safe dose limit for vMCO-I in human is estimated (based on ratio of dog to human eye vitreous volume being ~1:3) to be 1.92 E12 vg/eye of vMCO-I.
The proposed route of administration of vMCO-I is via single uniocular intravitreal injection. This is based on following: (i) intravitreal injection is a well-established minimally-destructive method for drug delivery to retina; (ii) anatomically isolated intravitreal delivery minimizes circulation of vMCO-I in other organs (as evidenced by the biodistribution study); (iii) Single uniocular injection further minimizes risks (if any) of inflammation in non-injected eye.

The vMCO-010 safety profile remains satisfactory and MCO-010 was well-tolerated 16 weeks after intravitreal injection. No serious adverse events observed in MCO-010 injected eyes or contralateral eyes and all dosed subjects continue active participation. Mild to moderate ocular inflammation and moderate increase in IOP in some subjects was treated with topical steroid and / or IOP-lowering drops. There was no itching, pain or redness of eye reported by the subjects. Furthermore, no significant change in retina thickness was observed at 16 weeks with respect to baseline as measured by OCT. The analysis of AAV2 neutralizing antibody 4 weeks after injection shows no detectable increase suggesting no systemic immune response.

Dose-response evidence of efficacy of vMCO-I through 16 weeks was observed including: (i) Improvement of outdoor light sensitivity and daily activities (ii) Improvements in visual acuity (iii) Decrease in light stimulation threshold (FST) (iv) increased visual field index in 30-2 Humphrey visual assessment (iv) decreased latency and improved score in Y and A-Mobility test (v) lowering of intensity/ size threshold as well as increase in accuracy of shape / direction detection and upper speed threshold for optical flow in Low Vision Multi-Parameter Test (LVMPT) and (vi) improvement in NEI-VFQ overall composite score as well as the three subscales scores on near activities, distance activities, and vision-specific dependency.
CONCLUSION

The overall preliminary safety and efficacy results from the phase I / IIa clinical study demonstrated that the benefit risk balance is strongly in favor of vMCO-I for the treatment of patients with vision loss due to RP. Intravitreal Optogenetic Gene Therapy in patients of Retinitis Pigmentosa with vMCO-I is well tolerated with no serious adverse events. Higher dose vMCO-I appears to improve visual acuity and visual function at 16 weeks compared to baseline measurements and demonstrates tremendous promise in restoring vision for retinitis pigmentosa patients.

REFERENCES


Colour Defective Student Doctor: A Reality Check With Clinically Applicable Test

Dr. Kirti Singh, Dr. Nikhil D Gotmare, Dr. Mainak Bhattacharyya

PURPOSE:

To evaluate the impact of color vision deficiency (CVD) in medical undergraduates by a more clinically applicable test.

METHODS:

Cross-sectional study of 31 students with CVD (Ishihara diagnosed) asked to identify subject-specific signs/tests requiring color identification on a customized medical multispecialty designed color album test (CAT). They were further subjected to Farnsworth D-15 testing.

RESULTS:

The error score of CVD students (4 ± 3.2) on 39 plates of color album test was highly significant as compared to the error score of color normal (0.3 ± 0.6). The CAT depicted linear correlation with Farnsworth D-15 and emerged as a valid tool of assessment. Ishihara interpretation did not correlate with the clinical impact of CVD. Nature of
error suggests that CVD students can anticipate problems in dermatology, pathology, hematology, microbiology, and biochemistry.

CONCLUSION

Color album test is a more clinically relevant test for CVD doctors to identify specialties where they can anticipate difficulties.

KEY WORDS

Color album test, color vision defective, Ishihara test.

INTRODUCTION

Medical students encounter various colored signs in clinical practice, such as pallor, icterus, and cyanosis. Persons with color vision deficiency (CVD) may have difficulty in assessment of these colored signs; alternatively, these signs may be missed, leading to wrong diagnosis and mismanagement of patients.\textsuperscript{[1,2]}

In the context of the health profession, color vision is not always tested nor is its deficiency a bar to qualifying or certifying exam of medical graduation. The guidelines change with some countries, such as India requiring color vision screening at the time of entrance to medical college without any counseling for career guidance or job options.

The test adopted for screening CVD has traditionally been Ishihara charts, sometimes aided with Edridge–Green lantern or Martin lantern.\textsuperscript{[3,4]} Those with higher grades on Edridge–Green lantern are considered eligible to pursue a medical specialization in India.\textsuperscript{[3]} Farnsworth D-15 test is sometimes resorted to in those with doubtful Ishihara scores.\textsuperscript{[5]}

However, for the medical profession, these guidelines extrapolated from recommendations for navigational personnel lead to a lack of contextual perspective regarding the ability of CVD doctors.
This is neither ethically nor technically correct as any screening test for fitness to practice should be combined with giving career advice, and timely diagnosis may permit early modifications in educational and other activities. [6]

The current need is to supplement or substitute existing color vision tools with objective, professionally contextual diagnostic tests. This would assist in the formulation of rational guidelines and ensure medical personnel with CVD adopt safe clinical practices. Our study by devising such a specialty-based color album sought to fill this need.

METHODS

This study was a cross-sectional, observational study conducted over the period from October 2016 to March 2018.

A color album consisting of 39 colored pictures, with 2–3 pictures detailing tasks or procedures requiring color discrimination pertaining to each specialty taught during medical training was generated by seeking the help of specialty experts [Table 1]. After obtaining clearance from the institutional review board and written informed consent from the study subjects, a total of 1500 (861 men) medical students studying at our institution were screened at the beginning of this study with the 38-plate edition Ishihara chart. Farnsworth

D-15 test was undertaken to classify the type of CVD into protans or deutans.

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<td><strong>Anatomy</strong></td>
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<td><strong>Pharmacology</strong></td>
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As per standard protocol, students who made three or more errors on Ishihara were considered color vision deficient; they were invited to volunteer for the study. To control for the degree of exposure to and degree of experience with laboratory and clinical work, an equal number of undergraduate students from the same batch who made no errors on Ishihara testing were invited to volunteer as controls. Students with CVD underwent examination to exclude ocular conditions known to cause acquired color vision deficiency (chorioretinal or optic nerve disease). The names, identities, and clinical data of students with CVD were kept confidential.

Students with CVD as well as controls were asked to independently (albeit in the presence of one of the authors) interpret the color-dependent clinical and laboratory photographs. Total error score (TES) for each task was noted.
When the proportion of students with CVD and color normals who made the error was the same, for both groups, the error was considered not to be related to CVD. However, when considerably more students with CVD made errors than controls from the same batch, we assumed that the errors were related to the CVD.

The Chi-square test was used to compare the proportion of cases and controls who made errors in assessing the individual colored clinical photographs. The quantitative variables in both groups were expressed as mean ± SD and compared using unpaired t-test between groups.

Pearson correlation was used to determine the relationship between errors on the Ishihara test and Farnsworth D-15 test, errors on Ishihara and errors on the color album, error score on D-15, and errors on the color album.

Comparison of errors among the CVD groups was done using Mann–Whitney U test and Kruskal–Wallis test. SPSS version 17 was used for statistical analysis.

RESULTS

Of the 1500 students screened (Ishihara chart); 42 (4.9 %), all men, were found to have CVD. Of these, only 31 consented to participate in the study, and an equal number of controls were enrolled. Most students with CVD (28/31; 90.3 %) reported that they were first diagnosed to be color vision deficient after admission to the medical course.

While students with CVD misread 08–30 slides on Ishihara testing (mean [SD]: 22.5 [5.5]), controls made no errors. Students with CVD made 0–10 errors in 39 color-dependent photographs (mean [SD]: 4.06 [3.20]), whereas color normal students made 0–3 errors (mean [SD] 0.29 [0.58]; P < 0.00).

To validate the new CA test, a correlation was done between errors made on Ishihara and those on the color album. A significant positive correlation was found with a Pearson correlation value of 0.55 (P = 0.001). The CA test was further validated by
correlation D-15 error score. This also showed a positive correlation with a Pearson correlation value of 0.779 (P = 0.000).

Severe CVD subjects made significantly more errors with deuteranopes making more mistakes than deuteranamalous subjects at 28:22 (on Ishihara), 39:25 (on D 15), and 15.6:2.4 (on color album). On comparing protans (protanopia) versus deutans (deuteranopia + deuteranomaly), more errors were done by protans on all three testing tools (Ishihara, D 15, and CA test). However, statistical significance was seen only on the CA test at P = 0.04 (Mann-Whitney U test). Deuteranomaly was the most common CVD detected at 61.3 % followed by Duteranopia at 19.4 %.

Students were asked to fill a questionnaire regarding their expectations and reservations about their medical career with their handicap. Quantitative analysis revealed a specific request for career counseling by 81 % of students, with the preferred time being during under graduation by 55 %. During such career advice 58.0 % wanted detailed advice regarding selection of branch for post graduation. All wanted to know about the adaptive strategies or help available to cope with CVD. Approximately 58 % perceived that screening done with Ishihara did not truly reflect the difficulties faced by them in their subjects and they conclusively agreed CA to be a more valid method in synchronous with their daily task.

DISCUSSION

The prevalence of CVD in our students, at 4.87 % among the male population, was lower than that reported from the general population (6 % – 8 %). The reason could be that our sample was from a limited institutional population.

On objective testing, students with CVD as well as those who were color normal made errors in the interpretation of colored signs. Maximal errors occurred in seeing shades of red during hematology (blood grouping and peripheral blood smear), Ziehl–Neelsen stain, in diagnosing melena, and in interpreting skin signs of lymphangitis, tinea, or
miliaria. In addition, red-blue differentiation in skin signs for the age of bruise, peripheral cyanosis, and green differentiation on identifying hemolysis on blood agar were the other problematic areas. Minimal errors occurred in interpreting mucous membrane signs, namely conjunctival pallor, Chadwick sign, pharyngitis, and otitis media, which involved the differentiation of shades of red and blue. Stereoscopic clues were a big help in reducing errors due to CVD.

The following is a detailed discussion on clinical situations where color clues assume significance [Table 2 and Fig. 1].

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<td>Acute Pharyngitis</td>
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<td>Amaranth dye/Calamine lotion</td>
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<td>12</td>
<td>Blood in stools</td>
<td>22</td>
<td>Acute Otitis media</td>
<td>13</td>
<td>Abrasion</td>
</tr>
<tr>
<td>27</td>
<td>Lymphangitis</td>
<td>24</td>
<td>Dengue rash</td>
<td>15</td>
<td>Vaccine Vail monitor</td>
</tr>
<tr>
<td>28</td>
<td>Conjunctival pallor</td>
<td>25</td>
<td>Cellulitis</td>
<td>16</td>
<td>Biomedical waste management</td>
</tr>
<tr>
<td>30</td>
<td>Peripheral cyanosis</td>
<td>29</td>
<td>Chadwick sign</td>
<td>17</td>
<td>Traffic signals</td>
</tr>
<tr>
<td>34</td>
<td>Tinea</td>
<td>31</td>
<td>Jaundice</td>
<td>19</td>
<td>KF ring</td>
</tr>
<tr>
<td>35</td>
<td>Milliaria</td>
<td>32</td>
<td>Fever with rash</td>
<td>20</td>
<td>Fundus (normal/pallor/cupping)</td>
</tr>
<tr>
<td>38</td>
<td>Gout (podagra)</td>
<td>33</td>
<td>EM target sign</td>
<td>36</td>
<td>IV cannula</td>
</tr>
<tr>
<td>39</td>
<td>Felon</td>
<td>37</td>
<td>Oropharyngeal airway</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Mistakes on photographs
Figure 1: Pictures on which moderate errors were made (4 or more): (a) ZN staining; (b) Peripheral blood smear; (c) Age of bruise; (d) Lymphangitis; (e) Peripheral cyanosis; (f) Tinea; (g) Miliaria; (h) Conjunctival pallor; (i) Melena

(A) Photographs depicting peripheral blood smear and blood identification

In these situations, CVD subjects made the most errors.

Ziehl–Neelsen’s staining of acid-fast bacilli recorded an interesting finding of most CVD students correctly identifying and counting the number of acid-fast bacilli; however, they confessed that they did not perceive them as red. Of these students, deutans faced the maximum difficulty in interpreting such slides correctly. The same finding has been corroborated by a study on 270 male histopathologists and medical practitioners.\[2,9\] However, researchers have opined that CVD does not impact the work in pathology as much, due to its primary
reliance on cell morphology and arrangement.\textsuperscript{[10]} The use of a magenta filter is of some benefit in those aware of their CVD while performing the histology work.\textsuperscript{[11]}

(B) Skin signs were especially difficult to be analyzed by CVD subjects viz. age of bruise, lymphangitis, peripheral cyanosis, tinea, and miliaria. For peripheral cyanosis and tinea identification, CVD subjects identified the abnormality with color perception differing, for them it was pink and green, respectively. In the skin slide depicting dengue rash, a protanope identified the pathology correctly but saw it as green. However, a deutan failed to identify it.

(C) Mucous membrane signs were also perceived to be difficult to be analyzed by CVD subjects, with conjunctival pallor detection having maximum difficulty. For interpreting acute pharyngitis or Chadwick sign of pregnancy, very few CVD students (<3) made errors. Difficulty in the perception of conjunctival pallor and mucous membrane inflammation signs has been concurred by prior researchers.\textsuperscript{[1,12,13]}

For acute otitis media, most subjects could correctly identify the abnormality; the reason for the same could be the inherent presence of stereoscopic clues in the picture. This concurs with previous studies showing that a CVD person does not face much difficulty in otoscopic examinations.\textsuperscript{[1,9,12]}

(D) Body fluids: Malena picture resulted in CVD subjects making significantly more errors than color normals in describing the abnormality. Some of the students could locate the abnormality but reported it to be appearing as green. This finding is consistent with Reiss et al.,\textsuperscript{[14]} who on studying the impact of color blindness on recognition of blood in body fluids found that the lowest rate of correct identifications occurred with pictures of stool and which correlated with the severity of CVD. Anecdotal report by a deutan general practitioner “I once
diagnosed a hematemesis as bile, the patient was lucky to survive” shows the extent of errors this can give rise to.

(E) Ophthalmological signs: Most CVD subjects were correctly able to identify and describe the abnormality in most of the photographs, namely KF ring, fundus normal / disc, and pallor/ glaucomatous disc. Only in the duochrome test and Worth 4 dot test did the students make a significant error with deuteranopes having more confusion. This is in variance to the report of a red-blind physician facing significant difficulties in ophthalmological signs.\(^{[15]}\) Contrast differences between pigmented and surrounding nonpigmented areas have been used by CVD optometrists to assist in defining abnormal areas.\(^{[16]}\)

(F) Colorimetric tests: Most CVD subjects were able to identify and describe abnormality, with only one student each of protanope and deuteranope making an error in Benedict and Seliwanoff test, respectively.

(G) The clinical situations in which subjects made no errors dealt with the following subjects: anatomy (spleen histology and thymus histology), pharmacology (amaranth dye/calamine lotion), preventive and social medicine (vaccine vail monitor, biowaste management, and traffic signals), and anesthesia (IV cannulas and oropharyngeal airway). These color tests can be stated color neutral, with students relying on knowledge and understanding to give the correct answer.

Concerning colorimetry, studies have shown that with the chromaticity of charts currently in use, no problem arises in detecting the presence or absence of glucose, and errors if any may occur only during quantitative testing.\(^{[17]}\) Safe clinical practices suggested while interpreting colored clinical signs included cues such as contrast, borders, surface, stereopsis use of adequate lighting, reliance on a detailed history, help of seniors, and employing noncolor dependent digital technology.
IMPLICATION AND LIMITATIONS

Our study confirmed that CVD medical students encounter significant problems in identifying color-cued diagnoses. Fields of dermatology, pathology, hematology, microbiology, and biochemistry could be challenging for such students. For clinical subjects such as pediatrics, medicine, and ophthalmology where color changes in skin, conjunctiva, and fundus are important indicators of disease, specific training needs to be imparted in the use of additional adaptive strategies.

The limitations of our study were the use of study photographs of color-dependent signs instead of real clinical situations. All tests were done under standard illumination, while such good illumination may not be present in real-life situations. Detailed history on ancillary clues was not provided; most studies state additional clues gleaned from a careful history aid in diagnosis.

The use of additional cues is probably inherent to persons with CVD even if they are not aware of the CVD. However, students unaware of the problem may not ask for help and instead doubt their learning ability. Timely detection along with counseling can aid students to adopt safe clinical practices and dictate informed career choices about post graduation specialty.

CONCLUSION

In the Indian context with CVD students debarred from pursuing the profession or from training in a specialty of choice, it is unethical to base this on noncontextual tests like Ishihara. A more clinically applicable test, like the CAT, should be resorted to.

Timely awareness and targeted counseling followed by practicing adaptive strategies to ensure patient safety can make these doctors enter mainstream jobs without guilt or fear. Our policies concerning the recruitment of medical professionals with CVD need to be overhauled and made realistic.
FINANCIAL SUPPORT AND SPONSORSHIP
Nil.

CONFLICTS OF INTEREST
There are no conflicts of interest.

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Prof. Dr. Alok Sati

PURPOSE:

Deep anterior lamellar keratoplasty (DALK) is effective in treating corneal disorders like keratoconus, dystrophy and scarring. Compared to penetrating keratoplasty, DALK minimizes the risk of endothelial rejection and assures similar outcomes in visual acuity. However, DALK is associated with multiple suture related complications including astigmatism. To overcome these issues, the current study is aimed to evaluate the outcomes of suture-less, pre-Descemetic DALK assisted by femtosecond laser (FL-DALK).

METHOD:

Prospective, non-randomized clinical study. Corneal scar extending up to deeper layer of cornea, baring posterior 50 micron in 10 eyes of 10 patients who underwent FL-DALK, were included in the study. Patients who had extensive superficial or deep vascularization involving more than 2 quadrants of the cornea were excluded from the study. All patients were evaluated for uncorrected distance visual acuity (UDVA) and best corrected distance
visual acuity (BCDVA), slit-lamp biomicroscopic evaluation, intraocular pressure measurement using Tono-Pen. Depth of the corneal opacity was assessed using slit-lamp biomicroscope and measured by anterior segment optical coherence tomography (ASOCT; Carl Zeiss Meditec AG, Jena, Germany) for all patients.

FL-DALK was performed using a VisuMax femtosecond workstation (Carl Zeiss Meditec AG). Initially, the donor cornea was mounted over an artificial anterior chamber, and the epithelium was removed manually by scraping. Based on the depth of the corneal opacity, as measured by ASOCT, parameters were set in the VisuMax femtosecond workstation to cut similar thickness and diameter, as planned for host lamellar surgery. Femtosecond parameters were, energy setting of 44 with a single spiral-out scan direction with a track distance of 4.5 mm, spot distance of 4.5 mm, and side-cut angle of 90 degrees. The recipient lamella was cut thereafter using similar parameters. Subsequently the donor tissue was transferred to the recipient bed and edges of the donor graft were aligned with the host cornea. This was then adhered with fibrin glue after appropriate apposition. A bandage contact lens (BCL) was applied at the end of the procedure. Outcome measures include BCVA, keratometry and complications.

RESULTS:

Mean age of 10 patients (6 male and 4 female) was 64.7 ± 17.7 years with a mean follow-up of 9.2 ± 2.0 months. Mean corneal thickness at thinnest site and mean depth of corneal scar was 376 ± 53 micron and 328 ± 51 micron respectively. Mean thickness/ diameter of donor and recipient lenticules were 370 ± 102 micron / 7.5 ± 0.2 micron and 325 ± 90 micron / 7.5 ± 0.2 micron respectively. Mean BCVA and mean astigmatism at 6 months postop were 0.47 ± 0.16 (log MAR) and 2.1 ± 0.16 respectively. No intra and postoperative complications were noted.
CONCLUSION:

Suture less FL assisted DALK is a novel technique with absence of suture related complications.

REFERENCES:


Next Generation Crosslinking (Cxl) Calculator For Titration Of Energy In Thin Keratoconic(Kc) Cornea

Dr. Ritika Mullick, Dr. Rohit Shetty, Dr. Pooja Khamar, Dr. Abhijit Sinha Roy

INTRODUCTION:

In view of the prevailing uncertainties related to the current state of the coronavirus pandemic, the eye banking activities have been affected detrimentally. There is a paucity of donor corneas which can be used for corneal transplantation in the cases of advanced keratoconus. By expanding the scope of corneal collagen cross linking, it may be possible to delay or decrease the requirement of keratoplasty. The purpose of our study was to evaluate the safety and efficacy of a calculator for crosslinking in corneas with thin pachymetry.

The NXT (New generation CXL for Thin Cornea) UV-A calculator customizes the fluence for cross linking (CXL) in thinner corneas. This calculator attempts to provide a technique to delay the need for keratoplasty by improving the safety of crosslinking in thin corneas.
METHODS:

It was a prospective longitudinal study in which 70 eyes of 70 patients were recruited. Before their participation in the study, a written informed consent was taken from all the patients in accordance with institutional guidelines of the Declaration of Helsinki.

The inclusion criteria was the presence of progressive keratoconus with a mean thinnest corneal thickness (TCT) < 400 µm. All patients included in the study were evaluated in detail for corneal tomography, epithelial mapping (CSO MS39) & specular microscopy. These tests were done preoperatively & postoperatively at one month, three months and six months after surgery. Lambart-Beer (LB) equation was used to build a simple calculator to decide the UV “on” time for an incident intensity of 3 and 9 mW/cm².

The mean corneal thickness after de-epithelialization was fed into a custom-built web-based calculator, customizing fluence time based on chosen UV power. The NXT calculator provides fluence times for UV power of 9 and 3 mW/cm². The clinicians can use the online calculator (https://jscalc.io/calc/VmanUJD6yQ13VQQ6) to calculate the fluence time at the time of surgery.

RESULTS:

There was an improvement in the postoperative best corrected visual acuity (p = 0.14). There was no significant haze noted on densitometry using Pentacam HR (p = 0.14). At 6 months postoperatively, all the patients had a stable topography, with no signs of progression.

Anterior segment optical coherence tomography showed the demarcation line at 3 months in 64% patients at a depth of 295 ± 71 µm. Postoperatively the endothelial cell density
remained unchanged on specular microscopy (p=0.83). Patients were fitted with contact lenses at the end of 3 months & achieved visual acuity of 20/20 or better.

CONCLUSION:

The NXT (New generation CXL for Thin Cornea) UV-A calculator is a simple tool to titrate the energy fluence. It is a freely downloadable calculator and its ease of use makes the calculator an important tool in the clinician armamentarium. Using this web-based calculator crosslinking can be performed in thin corneas with no additional tools.

KEYWORDS:

Crosslinking, keratoconus, thin cornea
INTRODUCTION

Sutureless anterior lamellar keratoplasty (SALK) is a lamellar corneal transplantation procedure for the treatment of corneal scars, limited to anterior 150 - 200 microns of cornea. SALK provides advantages of sutureless lamellar corneal surgery procedure to treat anterior corneal opacities. It can be performed either by using microkeratome where a particular thickness blade is used for cutting donor and recipient lamellar corneal buttons or by using femtosecond laser for programmed cutting of donor and recipient partial thickness corneal tissues as in femtosecond laser assisted sutureless anterior lamellar keratoplasty (FALK). One of the major concerns for ophthalmologists while performing SALK is sizing of appropriate donor and recipient cuts for achieving good apposition of graft host junction. We describe modified sutureless and glueless technique termed as ‘tuck in’ femtosecond laser assisted sutureless anterior lamellar keratoplasty (T-FALK) for management of anterior corneal scars.
METHODOLOGY

A total of fifteen eyes of fifteen patients with anterior corneal opacities, involving anterior 200 microns of cornea underwent T-FALK. T-FALK was performed using VISUMAX femtosecond workstation (Carl Zeiss Meditec AG, Jena, Germany). Initially, donor cornea was mounted over artificial anterior chamber and epithelium was removed by scraping. Based on depth of corneal opacity, as measured by ASOCT, parameters were fed in to the Visumax femtosecond workstation to cut similar thickness and diameter as was planned for host lamellar surgery. Femtosecond parameters used included energy setting of 36 with single spiral out scan direction with a track distance of 4.5 microns, spot distance of 4.5 microns and side cut angle of 45 degrees instead of conventional 90 degrees used in previous studies. Then recipient lamella was cut using similar parameters. No oversizing of donor tissue by 0.1mm was done as was suggested in earlier studies. Depth of donor lamellar cut was kept 10 % more compared to recipient lamellar cut to cater for any swelling in the cornisol preserved donor tissue. The epithelium was removed in donor corneas where epithelium was edematous or had epithelial defects, to achieve a uniform plane of dissection with femtosecond laser. Diameters of donor and recipient lenticules were kept similar and between 7.9 to 8.5 mm. All procedures were done under topical anesthesia using proparacaine hydrochloride 0.05 % eye drops. After cutting donor and host tissues, donor tissue was transferred to the recipient bed. After aligning the donor tissue over the recipient bed, edges of the donor graft were tucked under the host corneal margins all around 360 degrees as created by 45 degrees femtosecond sidecut. A bandage contact lens (BCL) was applied at the end of the procedure. Eye drop moxifloxacin hydrochloride 0.5 % was instilled after the procedure. All patients were advised eye drop prednisolone sodium phosphate 1 % four times a day and eye drop moxifloxacin hydrochloride 0.5 % four times a day for next three weeks. BCL was removed after three weeks. UCVA, BCVA and slit lamp biomicroscopic evaluation was done at each follow up visit. ASOCT was done to assess the healing and apposition of the graft at one day, one
month and three months. Eye drop moxifloxacin hydrochloride 0.5% was stopped after three weeks. Eye drop prednisolone sodium phosphate 1% was tapered to three times a day for next two weeks and twice a day for next two months.

RESULTS

A total of 15 patients (8 males and 7 females) underwent T-FALK using VISUMAX femtosecond workstation. Six patients had superficial corneal opacities following healed microbial keratitis, 5 patients had spheroidal corneal degeneration, 3 had Salzmann nodular degeneration and 1 patient had vortex keratopathy. The mean preoperative depth of corneal scar was 148 ± 9.4 microns and mean thickness of recipient scarred lenticule removed was 153.3 ± 9.0 microns. Mean thickness of donor lenticule was 168.7 ± 9.9 microns which reduced to 153.2 ± 8.8 microns, three months postoperatively as measured by ASOCT. Mean preoperative BCVA was 0.96 ± 0.093 logMAR units which improved to 0.53 ± 0.057 logMAR units three months after the procedure. The p value was 0.0006 and was highly significant. Postoperatively, refraction was possible in all patients suggesting clearing of visual axis and decrease in irregular astigmatism. Four patients where refraction was possible preoperatively, showed mild hyperopic shift in the spherical error (1.37D preoperatively to 1.5D postoperatively at three months) and decrease in astigmatism from preoperative mean value of 1.63D to 0.47D, 3 months postoperatively.

Fig 1

Fig 1
DISCUSSION

Femtosecond assisted-shaped corneal transplantation procedures are being increasingly performed due to availability of precise femtosecond laser cutting technology with ability to design full thickness as well as lamellar grafts with respect to margin or overall diameter. FALK offers many advantages over conventional microkeratome assisted SALK. It can be programmed for any precise depth or diameter of lenticule cut as opposed to microkeratome which has limitation of fixed diameter and depth. The graft host junction apposition in post SALK patient is variable and is theoretically considered to be better in FALK, compared to microkeratome assisted SALK.
In T-FALK, we have modified side cut angle to 45 degrees for both donor and recipient cut, keeping overall diameter same for both. When donor lenticule is placed on recipient bed, margins of the donor lenticule can be tucked under the recipient cornea providing overlap varying from 150 to 400 microns between two lamellar margins, depending upon the thickness of femtosecond lamellar cut. While on one aspect, it provides more surface area between two lamellar marginal surfaces to heal, it also covers for small mismatch between the donor or recipient lenticule size. There is no uneven surface as donor and host tissue are similar in overall diameter and side cut thus, providing better apposition and healing at graft host junction. Fig 2
As shaped corneal transplantation surgery is, probably, the way ahead for corneal transplantation procedures despite being technologically challenging and concerns of cost-effectiveness, suture-less and glue-less T-FALK may lead to further improvement in biomechanics at graft host junction following lamellar corneal transplantation for management of anterior corneal scars.
Glaucoma In Patients With Retinitis Pigmentosa

Dr. Zia Sultan Pradhan

INTRODUCTION:

There is a well-established association between Retinitis Pigmentosa (RP) and glaucoma. Western literature has shown that 2-12% of RP patients have primary open-angle glaucoma (POAG). [1] However, there is scant literature on the association between primary angle closure disease (PACD) and RP. [1-3] Also, the identification of glaucomatous damage in these RP patients is challenging as both diseases cause RNFL thinning on OCT and progressive peripheral visual field loss.

Glaucoma is a disease of retinal ganglion cell apoptosis and OCT of the macula has shown thinning of the ganglion cell layer in even early glaucoma. In contrast, RP is a disease of photoreceptor degeneration and predominantly shows OCT changes in the outer retinal layer of the macula. Therefore, our hypothesis was that in eyes with both RP and glaucoma, the inner retinal layers of macula on Spectral Domain- OCT imaging will be thinner when compared to eyes with RP alone.
The aim of the present study was to determine the prevalence of PACD in patients with RP. Additionally, we compared the thickness of different retinal layers on macular OCT in eyes of patients having both RP and glaucoma with those of RP alone.

METHODS:

This was a retrospective review of the electronic medical records of all patients over the age of 18 years with RP attending a Genetics Eye Clinic between April 2012 to June 2019. The study was performed in compliance with the Declaration of Helsinki and was approved by the Institutional Review Board and Ethics Committee.

All patients attending the Genetics Eye Clinic underwent a thorough medical history, family history and pedigree charting and complete ocular examination including vision, refraction, slit-lamp examination, intraocular pressure (IOP) measurement, and dilated fundus examination with a 90 D lens. All patients attending the Genetics eye clinic also underwent a macular SD-OCT examination (Spectralis, Heidelberg Engineering, Germany) and visual fields examination (Humphrey Field Analyzer II, model 720i, Carl Zeiss Meditec, Inc. Dublin, CA, USA) when possible. The demographic data (age, gender, presence of systemic illnesses like diabetes mellitus and hypertension, refractive status, lens status, IOP) of all RP patients was retrieved. RP was defined based on clinical fundus appearance (waxy disc pallor, bony spicules, attenuation of blood vessels, etc) and confirmed on ERG in case of atypical fundus picture. All patients with a shallow anterior chamber, IOP greater than 21 mm Hg or cup:disc ratio > 0.6 were referred to the glaucoma department for the opinion of a glaucoma specialist. Here, additional IOP measurements, gonioscopy using a 4 mirror goniolens, and an optic disc evaluation was performed. This supplementary data, as well as information regarding glaucoma treatment (medications, lasers or surgery) was also included for analysis. Other details collected were type of RP and mode of inheritance. Patients with retinal dystrophy other than RP and patients under 18 years of age (as they may not co-operate for a complete eye examination) were excluded.
The following definitions were used to classify patients referred to the glaucoma clinic:

Primary angle closure suspect: >180 degrees of iridotrabecular contact (ITC), IOP < 21 mm Hg, and cup:disc ratio d ≤ 0.6.

Primary angle closure: >180 degrees of ITC with peripheral anterior synechiae (PAS) or IOP > 21 mm Hg, and cup:disc ratio d ≤ 0.6.

Primary angle closure glaucoma: >180 degrees of ITC, IOP > 21 mm Hg, and cup:disc ratio d ≤ 0.7.

Primary open-angle glaucoma: Open angles, IOP > 21 mm Hg, and cup:disc ratio d ≤ 0.7.

Secondary glaucomas: IOP > 21 mm Hg with an identifiable secondary cause.

In additional to the prevalence data, the macular SD-OCT of cases (RP with glaucoma) were compared with controls (RP alone). Cases were defined as eyes with RP which had an IOP > 21 mmHg on Goldmann applanation tonometry with or without glaucomatous changes. Controls were RP patients with IOP d ≤ 21 mm Hg. Cases and controls were matched for visual acuity and central foveal thickness. For this part of the analysis, the exclusion criteria were eyes with previous ocular surgery (except uncomplicated cataract surgery), cystoid macular edema, epiretinal membrane, any form of maculopathy and poor signal strength of OCT scans (< 20).

The segmentation software on the Spectralis OCT was used to study each layer at the macula. This divides the macula into 4 perifoveal and 4 parafoveal sectors around the fovea (ETDRS grid). This software can analyse individual layers at the macula and give the thickness and volume of each sector. It also provides the thickness of the inner retinal layer (IRL) measured from the internal limiting membrane (ILM) to the external limiting membrane (ELM). The outer retinal layer (ORL) is measured from the ELM to the Bruch’s membrane.
Statistical analysis was performed using Stata version 14.2 (StataCorp, College Station, Tx). Mean with standard deviation (SD) was calculated for continuous variables and frequency with percentage (%) were tabulated for categorical variables. The t-test was used to compare the retinal thickness between the groups. A p value \( p \leq 0.05 \) was considered statistically significant.

RESULTS:

The electronic medical records of 618 RP patients were analysed. Based on the definitions of glaucoma, 1.3% had POAG and 2.3% had primary angle closure glaucoma (PACG). In RP patients over 40 years of age, the prevalence of PACG was 3.8%.

In the analysis of macular OCT, 21 eyes of 13 patients with glaucoma and RP were included as the cases. These were compared with 26 control eyes of 24 RP patients with no evidence of glaucoma. The glaucomatous patients included 8 POAG and 13 PACG eyes. There was no significant difference in the age, gender, visual acuity or refraction between the cases and controls. The Median IOP was 13.5 (IQR 11.5,16.5) mmHg in the control groups and 24.0 (IQR 16,29) in the cases (\( p = 0.018 \)). Also, the cup: disc ratio was significantly higher in the cases (0.77 ± 0.19 vs 0.33 ± 0.13, \( p < 0.0001 \)). The visual field parameters (mean deviation and visual field index) were similar between the groups. The central foveal thickness was similar between the groups (259.9 ± 43.7 and 270.5 ± 49.7, \( p = 0.44 \)). There was no difference between the total retinal thickness of the 2 groups in any of the ETDRS sectors. The ganglion cell complex (GCC) layer of the inferior (70 ± 17 vs 83 ± 21) and nasal (84 ± 30 vs 101 ± 21) perifoveal sectors were significantly thinner (\( p < 0.05 \)) in the patients with RP and glaucoma compared to the controls. The outer retinal layers had a similar thickness in both groups.
DISCUSSION:

This study determined the prevalence of angle closure in an RP population. There is limited literature on the prevalence of angle closure disease and RP. [1-3] In the present study, the prevalence of PACG in RP patients over the age of 40 years was 3.8 % which is higher than the prevalence measured in population-based studies in India (0.8%). [4] This strong association between RP and PACG warrants a careful and thorough examination, including gonioscopy, in all patients with RP.

There is a lot of literature on the GCC thinning in glaucoma since retinal ganglion cells (RGCs) are the predominant cell affected in the disease. [5] Interestingly, studies have also shown GCC thinning in RP. [6] There are 2 main theories put forth to explain this finding. One is the photoreceptor degeneration causes reduced transsynaptic signals and secondary RGC loss. The other theory is that the reduced blood flow to the inner retinal layers causes RGC degeneration and GCC thinning. The literature on imaging in RP and glaucoma is sparse and this is the first study evaluating the retinal layers on macular SD-OCT in this cohort. We found that the GCC layer in the perifoveal regions is significantly thinner in eyes of RP patients with glaucoma despite the total retinal thickness being similar. Hence, the GCC may be a biomarker for glaucoma in eyes with RP and a detailed segmental assessment of these retinal layers should be performed in eyes with RP suspected of having glaucoma. Future longitudinal studies of these patients should be done to monitor progressive changes in the macula on SDOCT.

CONCLUSION

This study has shown that gonioscopy is warranted as part of the routine examination in RP patients. Eyes with RP and glaucoma have a thinner GCC layer in the perifoveal region. Hence, GCC thinning is a potential biomarker of glaucomatous damage in RP.
REFERENCES:


Comprehensive Approach In Exploring Therapeutic Potentials In Retinal Dystrophies

Dr. Poornachandra B

INTRODUCTION

Retinal dystrophies (RD) are progressive and one of the major causes of untreatable blindness in both eyes. It is characterized by retinal degeneration including loss of retinal pigment epithelial cells and photoreceptors [1]. Studies [2] have shown that highest level of heterogeneity, approximately 250 genes and their mutations were associated with various forms of RD. Clinical manifestations range from mild (night blindness) to severe visual impairment, even with early onset (Leber congenital amaurosis) of retinal degeneration. The most common form of inherited RD is Retinitis pigmentosa (RP) with a prevalence of 1 in 3500 – 4000 individuals. It can be inherited through a dominant mode (adRP) or autosomal recessive (arRP), or an X-linked mode of inheritance (XIRP) [3,4]. It affects mainly the photoreceptor cells in the retina, rapidly progressive at younger age of onset in arRP form, but adRP patients show a late onset associated with clinically less severe form [3,4]. Cone rod dystrophies (CRDs) affect the impairment of vision at early
adult life in 1/40,000 people. Clinical symptoms include colour vision problem, decreased central vision due to loss of cone function followed by night blindness and defect in the peripheral visual fields because of rod dysfunction[5]. Leber congenital amaurosis (LCA) (OMIM # 204000) is a prenatal or early-onset childhood inherited retinal dystrophy associated with poor vision, and severe retinal dysfunction involving rods and cone cells, that detects light in the retina. Another frequent childhood or adolescence macular dystrophy is Stargardt disease (STGD) with a frequency of 1 in 50,000. ABCA4 gene mutations were found to be most frequent in autosomal recessive forms. Congenital achromatopsia is an isolated cone dystrophy, which is inherited in an autosomal-recessive mode and causes complete loss of cone function, whereas rod functions were maintained properly throughout the disease course.

RD are often misdiagnosed due to genetic complexity and overlapping clinical phenotypes. To develop new therapeutic approaches and accurate genetic counselling of affected patients and their family members, it is important to know the detailed clinical diagnosis and genotype-phenotype correlations.

MATERIALS AND METHODS

This was an observational study. Informed written consent either from the patient or the guardian and family members was documented. A total of 45 patients with hereditary retinal dystrophies from unrelated families from India were investigated. Age at the time presentation ranged between 5 – 31 years (median - 18) with Male : Female = 31 : 14. We performed targeted next-generation sequencing (NGS) in clinically confirmed 21 unrelated patients with different forms of RD and their selected family members using retinal dystrophy panel which covered previously associated genes with retinal disease. Sequencing results were analyzed by read mapping and variant calling in genes of interest, followed by their verification and interpretation.

The prospective study was approved by the Institutional Review Board and was performed
as per institutional ethics guidelines and in accordance with the tenets of the Declaration of Helsinki. Subjects were recruited for the study after obtaining informed written consent either from the patient or the guardian and family members. A total of 21 patients with hereditary retinal dystrophies from unrelated families from India were investigated. Age at the time presentation ranged between 5 – 31 years.

Detailed medical history was obtained, followed by clinical examination including best-corrected Snellen visual acuity (BCVA), slit-lamp examination, Gonioscopy, indirect ophthalmoscopy and fundus photography. Fundus autofluorescence (FAF) imaging with a confocal scanning laser ophthalmoscope (Spectralis, Heidelberg Engineering, Heidelberg, Germany) in all patients and selected family members was performed. Spectral domain optical coherence tomography (SD-OCT; Spectralis, Heidelberg Engineering, Heidelberg, Germany) was also performed simultaneously in most of these patients and in pediatric cases a handheld SD-OCT (Envisu 2300, Bioptigen, DNC, USA) was performed. Electrophysiologic examinations were conducted according to the standards given by the International Society of Clinical Electrophysiology in Vision. 18, 19 Viking 5.0 Ganzfeld dome (Nicolet Biomedical Instruments, Madison, Wisconsin, USA) with a light-emitting diode for light stimulation was used for both electro-oculography and full-field electroretinography in selected patients. Sequencing results were analyzed by read mapping and variant calling in genes of interest, followed by their verification and interpretation.

RESULTS AND EXPERIMENTAL ANALYSES

The sequencing analysis revealed a total of 45 different mutations in patients with RD including Leber’s congenital amaurosis, cone-rod dystrophy, Retinitis pigmentosa, Achromatopsia and Stargardt’s disease. Among these nine mutations were unreported and fourteen variants were previously associated with RD. These nucleotide changes
were not present in 100 normal controls analyzed. We add nine novel mutations with existing spectrum of gene mutations identified in Indian patients with the characteristic features of RD, which provide further information on the genotype/phenotypic correlation.

Detailed molecular and functional analysis of the genetic variants is critical to further our understanding of the disease process and clinical prognosis (6). Further, treatment of IRDs requires gene therapy approaches. Several studies are therefore underway using a variety of retinal dystrophy animal models to establish their efficacy (7). The gene delivery modality of choice is recombinant AAV vector, expressing the therapeutic genes. These are typically delivered by the sub-retinal route, followed by functional analysis between 6-12 weeks post transduction. AAV mediated delivery can transduce RPE as well as photoreceptors. (8)

A comprehensive approach is important to diagnose and label hereditary RD. This will help to guide patients regarding the prognosis, lifestyle modification and not to mis-label treatable conditions as dystrophies. Our initial mouse model based experiments will also help to guide familial or isolated patients with Retinal Dystrophies about future prospects of gene therapy.

REFERENCES


Infectious Scleritis: Changing Profile In A Tertiary Eye Care Centre

Dr. Bidisha Mahapatra

ABSTRACT:

AIM:

To study the clinico-microbiological profile and treatment outcome of infectious scleritis.

METHOD:

All cases of infectious scleritis between January 2016 and December 2019 were reviewed and demographical, clinico-microbiological data and treatment outcome was analysed.

RESULTS:

12 cases of infectious scleritis were identified. All except 4 cases had history of trauma (41.6 %) or cataract surgery (25 %). Redness with pain was most common presenting complaint. Most common causative organism was fungus (50%, n = 6), followed by Pseudomonas (25%, n = 3). Microbe specific medical treatment and scleral debridement
was done for all cases. Globe was preserved in 83.3% cases. 41.6% had BCVA e6 / 18 at the end of 3 months.

CONCLUSION:

Trauma is the commonest predisposing factor for infectious scleritis followed by surgery. Fungi are the commonest causative agent followed by Pseudomonas. Early surgical debridement helps in early identification of the organism and reduction of infective load, thus playing a major role in visual and anatomical success.

KEYWORDS

Infectious; scleritis; trauma; fungal

INTRODUCTION

Scleritis refers to a severe painful inflammatory condition of sclera, which may involve cornea, uveal tissue and adjacent episclera. Scleritis due to infective etiology is a rare entity and accounts for 5–10 % of all cases of scleritis 1. The initial clinical picture of infectious scleritis may be identical to that caused by immune-mediated scleritis. Therefore, in a patient presenting with scleritis, an infectious etiology is often not suspected resulting in unusual delay in the diagnosis and consequently worsened outcome. Infectious scleritis may follow accidental or surgical trauma, severe endophthalmitis, or may occur as an extension of a primary corneal infection 2. Systemic illness, use of corticosteroid and immunomodulators or previous history of scleritis may also be predisposing factor 3. Pseudomonas aeruginosa has been the most commonly reported causative agent in various series followed by fungus 4 - 6. Other causative organisms like Staphylococcus species, Streptococcus species, Hemophilus influenza, Stenotrophomonas maltophilia, Serratia marcescens, Mycobacterium species,
Mycobacterium species, Nocardia, fungus, and virus have also been reported. However, reports from India have stated fungi to be more common in tropical regions. Sclera being an avascular structure with dense collagenous framework, limits the penetration of traditional topical antibiotics. The clinical outcome in cases of infectious scleritis is generally poor and most cases required evisceration in many series. Also, very often misdiagnosis of autoimmune scleritis or post surgical inflammatory scleritis with vigorous corticosteroid regime worsens the condition and delays timely intervention. But, a review of more recent reports clearly suggests that if early diagnosis is combined with prompt institution of antibiotic therapy and early surgical intervention, infectious scleritis can be managed successfully with good visual and anatomical outcome.

MATERIALS AND METHODS:

We retrospectively reviewed the medical and microbiological records of all patients with microbiologically proven infectious scleritis examined from January 2016 to December 2019 in department of Cornea and Refractive surgery services in our hospital. Information including patient’s age, gender, the predisposing factors, pathogenic organisms, duration of presentation, clinical presentation, methods of diagnosis, treatment, and outcomes were abstracted from the medical records. At presentation, all patients were examined in detail underslit lamp. With proper consent of patient, suspected infective scleral lesions with ulceration were subjected to scraping with scleral knife under topical anaesthesia and smeared on glass slides for Gram’s staining and Potassium hydroxide mount. All the cases were subjected to incision and drainage with scleral debridement under peribulbar anaesthesia in the operating room. Materials collected from the lesions were smeared on glass slides and stained with Potassium hydroxide and Gram’s stain and were sent for culture on blood agar, chocolate agar, potato dextrose agar (PDA) and nonnutrient agar with an Escherichia coli overlay. Significant growth was defined as confluent growth on solid media, and/or growth of the same organism on
more than one medium, and / or growth in one medium was accompanied by presence of similar organism in smears. Microbiologically culture-proven cases of scleral ulcer and / or abscess were included in the study, while cases with no growth in culture were excluded from the study. All bacteria and fungi grown were identified and were tested for antibiotic susceptibility by Kirby-Bauer disc diffusion method. Initial therapy was based on either the clinical suspicion or results of microscopic examination of smears. Treatment was later modified depending on the clinical response and the results of culture and sensitivity. Resolution was defined as absence of symptoms, congestion, or active infiltrate.

RESULTS

We included 12 cases (12 eyes) of infectious scleritis, among which 9 were males and 3 females (Demographic features, clinical presentation and etiology are detailed in Table I, treatment and outcome are detailed in Table II). Age ranged from 32 years to 76 years (mean 52.4 ± 13.3 years, median 49.3 years). The mean duration from onset of symptoms to presentation was 12.16 ± 9.5 days (range of 4 to 30 days). The mean follow up period was 16.3 ± 14.4 weeks (range of 3 to 46 weeks). Average time taken for healing of lesion with appropriate treatment was 4.9 ± 3.2 weeks (range of 1 to 12 weeks).

Trauma was the most common predisposing factor (41.6%, n = 5) followed by previous history of cataract surgery (25%, n = 3), all of which were manual small incision cataract surgery. In 4 patients (33%), no history of trauma or surgery could be elicited, but all these cases were on topical steroids for a prolonged duration before presenting to us. The interval from trauma to presentation of infectious scleritis ranged from 4 days to 1 month (mean = 19.6 days), while that of preceding ocular surgery to presentation ranged from 15 days to 6 years. Six patients (50%) were using topical corticosteroids at the time of reporting to us. Out of twelve patients only 1 had diabetes mellitus while the remaining eleven patients didn't have any significant systemic illness. Most common presenting
symptoms were redness (83%) and moderate to severe pain (in all the cases) in the affected eye. The presenting visual acuity varied from light perception present (PL positive) to a normal vision of 6/6. Five (41.6%) patients presented with a visual acuity of 6/60 or worse.

Microbiological profile included fungus (50%, n = 6), Pseudomonas aeruginosa (25%, n = 3), Nocardia (n = 1), Staphylococcus species (n = 1) and Klebsiella species (n = 1). One was a case of mixed Aspergillus and streptococcal viridans infection (Case 5). Aspergillus species was the commonest (83%, n = 5) of all fungal isolates. Nodular scleral lesion with pus point (Fig 1) was the commonest (n = 11, 91.6%) presenting sign except one with scleral wound melt at scleral tunnel site (case 12). Corneal involvement was seen in 16% cases (n = 2) and pseudomonas was the causative organism in both the cases. Multifocal abscess was noticed in 25% (n = 3) cases at presentation and 16% (n = 2) cases presented as unifocal abscess and progressed to multifocal during the course of treatment (fig 2). Severe anterior chamber reaction was seen in 4 cases (33%).

All cases underwent scleral debridement except one case who had post cataract surgery wound melt (fig 3). 25% (n = 3) cases underwent multiple debridements due to recurrence at different location of sclera during the course of treatment. The surgical debridement was diagnostic in all cases. This also facilitated debulking of the infected scleral tissue and improved the drug penetration. During the surgical debridement, the actual area of involvement was usually found to be larger than that visible on slit lamp examination. One case (Case 12) with post small incision cataract surgery scleral wound melt received scleral patch graft as primary procedure along with intraocular antibiotic in view of suspected post operative endophthalmitis.

All cases with proven fungal etiology were treated with topical natamycin and topical fluoroquinolones, with additional systemic antifungal drugs, in case of poor response. All cases due to culture-proven bacterial etiology were treated with topical antibiotics.
and systemic medication, based on antibiotic susceptibility testing (Table III). All cases of proven pseudomonas infection received intravenous amikacin, while staphylococcal infection received oral ciprofloxacin. Tapering doses of topical steroids, was given in scleritis of bacterial etiology after active infection had subsided. 83% (n=10) of cases had complete resolution of infection and globe architecture was preserved, while 2 eyes underwent evisceration. Posterior segment examination with B scan ultrasound was normal in all the eyes except one eye with panophthalmitis (case 12).

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Table III: Antibiotic susceptibility of isolated organisms (Kirby Bauer disc test)
Among the eyes which underwent evisceration, one patient (case 1) (Fig 4) with culture proven fungal infection, showed poor response with antifungal treatment, progressed to develop secondary glaucoma and painful blind eye and had to be eviscerated. Another case (case 12) with post cataract surgery scleral melt underwent scleral patch graft and intravitreal antibiotics, but subsequently developed panophthalmitis and was eviscerated. Three (25 %) cases resolved with progression of cataract while one among them was complicated with choroidal detachment during the course of treatment which resolved with oral steroids.

In our series, 41.6 % (n = 5) patients had final best corrected visual acuity (BCVA) of better than 6/18 while 25 % (n = 3) had worse than 6/60 and 33 % (n = 4) had fair visual outcome in between <6/18 and 6/60. 71% of patients with presenting BCVA better than 6/60 had improved to 6/18 and better.

**DISCUSSION**

As reported earlier, trauma or prior history of ocular surgery raises the suspicion of infectious scleritis in all cases of scleral inflammation presenting as scleral abscess or ulceration. Pterygium excision has been reported to be the most common surgical procedure in many series. Cataract surgery was seen to be the commonest in another series. In our series, 50 % cases had trauma while 25 % cases had history of cataract surgery, while no case of prior pterygium surgery was seen. This difference of more number of cases due to trauma in our series may be due to rural and agricultural background of our patients. Compared to rest of the world, small incision cataract surgeries are more often performed in India, which accounts for it being the most common ocular surgery responsible for the same. It is unusual for the scleral site to be infected long after surgery but surgical induced necrotising scleritis (SINS) has been seen to be occur long after surgery. Lin et al postulated that after initiation of SINS, microorganisms caused late onset post-surgical infective scleritis. One of the cases in our series had post SICS
wound melt with infiltrate (case 12). Melt in this case may be attributed to infective agent rather than SINS. None of our patients with late onset scleritis, had systemic vasculitis. Similar experience was reported by Altman et al13 and Jain et al1 in their case series. Meallet in 2006 proposed that the use of adjunctive therapies such as mitomycin and beta irradiation also likely compromise the integrity of episcleral conjunctival vessels and underlying tissue, inhibiting adequate wound healing and leaving the sclera vulnerable to infection14. Often corticosteroids given before diagnosis of infective origin, has been seen to increase the infection1. In our series, 6 cases had history of steroid use. With no predisposing history of trauma or surgery, immunosuppression due to human immunodeficiency virus or chemotherapy, may be a risk factor for spontaneous cases of infectious scleritis 4,15. There were 4 cases in our series with no predisposing trauma or surgical history. None of the four cases had any endogenous focus of infection or immunosuppression, but were under prolonged usage of topical steroids.

Pseudomonas aeruginosa is reported as the most common causative organism and rarely fungus for infective scleritis 4,5,16. Infection due to fungus, mostly Aspergillus, was found to be commonest in our series. In India, fungus is reported to be the most common in many series with Aspergillus species being the commonest causative agent 1,9,11. High incidence of fungal infection in India is due to agriculture being the most common occupation among the population and the tropical hot and humid climatic conditions. Infective scleritis often presents with multifocal nodules, Pseudomonas being most commonly reported with such presentation due to its proteolytic activity leading to intrascleral dissemination 4,5,6,9. In another series1 all cases of multifocal presentation were due to fungi. Our case series saw multifocal abscess (25%) at presentation in both pseudomonas (n = 2) and fungal scleritis (n = 1). Some studies have reported 1,4-6, that multifocal presentation is due to the load of infection and not due to the organism causing it, which can be well correlated to our findings.
As in autoimmune scleritis, patients with infectious scleritis commonly present with redness, pain, and epiphora. Mild to moderate pain is generally associated with diffuse and nodular scleritis whereas severe pain is more frequently associated with necrotizing scleritis, suggesting that pain out of proportion to examination findings may indicate underlying possible infectious etiology. Hodson KL et al reported scleral necrosis (93%) as the most common clinical sign, 67% had involvement of adjacent ocular structures like cornea and extraocular muscle. An anterior chamber reaction greater than 1+ grade is usually present at the initial encounter. In our series, 33% (n = 4) had anterior uveitis and 16% (n = 2) had corneal infiltrate. Endophthalmitis has also been documented as the presenting finding. Progressive inflammation leads to pupillary membrane, cataract, glaucoma, retinal and choroidal detachment and endophthalmitis. In our series 25% cases resolved with cataract, other complications being choroidal detachment (n = 1), absolute glaucoma (n = 1) and panophthalmitis (n = 1).

Pyogenic infection of sclera are difficult to treat because of poor antimicrobial penetration. Abscess exploration with systemic and topical antimicrobial therapy yields superior results. Some studies found that surgical debridement improves visual outcome while some showed that it shortens the course of treatment. Pradhan ZS et al showed that chances of globe preservation was better with prompt surgical debridement. Medical therapy was adequate as the sole treatment in only 18% of patients, with most requiring surgical debridement in a large case series studied by Hodson KL et al. A higher rate of enucleation or evisceration was seen in those treated solely with medical methods. Tittler et al showed a 100% globe preservation rate, with fewer complications and shorter hospital stays with prompt surgical debridement at diagnosis. We did surgical debridement within a mean duration of 6 days for all our cases expecting a better outcome in terms of globe preservation and were able to achieve the same in 83% of the cases. Scleral patch graft was done in one case (case 12) in view of large defect.
post scleral debridement. In addition to surgical debridement and topical and systemic antibiotics, adjunctive procedures such as subconjunctival injections of antibiotic at both ends of the scleral lesion, and wound irrigation with antibiotic solution one to two times a day followed by normal saline after improvement was shown to be beneficial. Meallet could achieve success in treating 6 cases of infective scleritis with use of continuous subpalpebral lavage antibiotics. In our series, betadine 5% lavage was done in all cases after scleral debridement. Review of literature revealed poor outcome in cases of fungal scleritis, while 2 studies showed good outcome in fungal scleritis with prompt surgical debridement and medical management similar to our study. Useful vision of 6/60 was retained in 61% eyes in series by Hsiao et al, 33% by Jain V et al and 83% by Sahu SK et al. Vision 6/60 was retained in 75% of our patients. 71% of eyes with presenting visual acuity of >6/60 improved to 6/18 and better. 4 out of 18, 3 out of 21 and none out of 17 eyes underwent evisceration in the above studies respectively. 2 out of 12 eyes underwent evisceration in our series. None of our cases showed recurrence once infection resolved completely, though 3 cases underwent multiple debridements during active infection. Though the appearance of recurrences after achieving full resolution of scleritis is generally rare, still cases should be closely followed up for an extended period of time after resolution.

CONCLUSION

Trauma is a common predisposing factor for infectious scleritis apart from ocular surgery. Fungus is the most common organism responsible for infectious scleritis followed by Pseudomonas in countries with agricultural occupational background. Though difficult to differentiate from autoimmune scleritis, subtle differences in clinical features highlighted above should be kept in mind while dealing with any case of scleritis. Any case of scleritis worsening with steroid use, should raise high suspicion of infective etiology. Prompt surgical debridement along with medical treatment plays a major role.
in early identification of infective agent as well reducing the infective load, thereby helping in attaining good visual outcomes and better chances of preservation of the globe.

REFERENCES


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<td>GNB</td>
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M- multifocal, U- unifocal, SA-scleral abscess, ND- not done, GPC- Gram positive cocci, GNB- Gram negative bacilli, org- organism, Y-yes

Table 1: Demographic Features, Clinical Presentation and etiology.
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SD-scleral debridement, *- multiple debridements, TMX-SMZ- trimethoprim sulphamethoxazole, E-evisceration, R-resolved, IOAB-intraocular antibiotics, SPG-scleral patch graft, cryo= cyclocryotherapy, RCS thickening = retinochoroidal scleral thickening, ST fluid= subtenon’s fluid

Table II: Treatment and outcome
A Novel Ab Interno Technique Of Aadi Tube Sulcus Placement: Initial Outcomes

Dr. Sanjana Rao

ABSTRACT:

AIM:
To report the initial clinical outcomes of a new technique of insertion of the silicone tube of the AADI in the posterior chamber sulcus

METHODS:
Non-comparative, interventional case series. Nine eyes of nine patients, with a follow-up of at least 3 months who underwent sulcus implantation of the AADI tube by the new technique between 2019 and 2020 were included. Control of intraocular pressure (IOP), number of pressure-lowering medications, visual acuity and surgical complications were recorded.
RESULTS:

Nine eyes of nine patients (mean (range) age 57.22 (45–66) years) were included in the study. The IOP was reduced from a preoperative mean (SD) of 28.33 (9.80) to 11.56 (2.65) mm Hg at 3 months. The mean (SD) number of preoperative medications for IOP control was reduced from 3.0 (0.7) to 0.4 (0.9) medications in the same period. There were no intraoperative complications noted.

CONCLUSION:

This technique of placement of the silicone tube in the posterior chamber sulcus is a safe and effective alternative to existing procedures of sulcus placement limiting multiple blind entries and thereby, preventing damage to adjacent angle structures.

INTRODUCTION

Glaucoma drainage devices (GDD) have attained popularity as the procedure of choice in refractory glaucomas. The commonly used GDDs today include the Ahmed glaucoma valve (AGV; New World Medical, Rancho Cucamonga, CA, USA), Baerveldt glaucoma implant (BGI; Advanced Medical Optics, Santa Ana, CA) and recently, the Aurolab aqueous drainage device (AADI; Aurolab, Madurai, India). The AADI implant is a newer non-valved GDD derived from the Baerveldt prototype which has demonstrated good long term control of IOP in numerous recent studies.

The commonly reported complications of any GDD include, postoperative hypotony, excessive capsular fibrosis, tube erosion and plate migration, strabismus and rarely endophthalmitis. However, the most significant long term complication of tube shunt insertion into the anterior chamber is corneal endothelial damage. Accurate placement of the tube away from the cornea is hence essential. The techniques of tube insertion into the ciliary sulcus and pars plana have been increasingly performed in pseudophakic and
aphakic eyes respectively to evade this complication. Although pars-plana vitrectomy is relatively safe when performed by experienced hands, vitrectomy and tube insertion into the posterior segment carries significant risks of retinal detachment, endophthalmitis, vitreous haemorrhage and vitreous incarceration in the tube lumen.\textsuperscript{10,11}

The ciliary sulcus is an anatomic space of potential importance for tube insertion especially in pseudophakic patients due to its expansion in anterior–posterior length following cataract extraction owing to the smaller diameter of the intraocular implant as compared to the crystalline lens.\textsuperscript{9} Studies have reported tube placement in the ciliary sulcus to be a safe and effective procedure offering adequate IOP reduction and reduced endothelial cell loss.\textsuperscript{9,12} The commonly employed technique described for sulcus placement of the GDD tube involves a relatively blind procedure of entry 1.5 to 2.5 mm away from the limbus directed towards the sulcus with prior insertion of viscoelastic.\textsuperscript{9,12}

However, bleeding in the anterior chamber, trauma to the iris, ciliary body and zonules, intraocular lens (IOL) displacement and inaccurate entry behind the IOL are potential complications to this procedure hence, needing longer learning curve.

In this article, we report the initial clinical outcomes of a novel technique of sulcus placement of the silicone tube of the Aurolab aqueous drainage implant (AADI) in pseudophakic patients as an alternative to the conventional method.

**PATIENTS AND METHODS**

The retrospective case series was conducted in accordance with the tenets of the Declaration of Helsinki of 1975 after getting approval from the Institutional Review Board and ethical clearance from the Ethics Committee. The nature, risks and possible adverse consequences of the procedure were explained to patients and consent taken from them. A single surgeon (DM) performed the procedure at the centre (Aravind Eye Care System, Tirunelveli, Tamil Nadu, India).
The charts of patients more than 16 years of age undergoing AADI insertion in the posterior chamber sulcus by the new technique and having at least 3 months of follow-up between July 2019 to January 2020 were reviewed. All patients with pseudophakia or those who underwent cataract extraction and intraocular lens placement at the time of the AADI implantation were included. Patients were selected for AADI surgery on the basis of uncontrolled intraocular pressure (IOP) after maximally tolerated medical treatment. Primary AADI implantation with or without combining phacoemulsification with intraocular lens implantation was carried out in all patients. The reason for the same was owing to the scarred conjunctiva from previous small incision cataract surgery with PCIOL implantation, secondary glaucomas such as neovascular glaucoma (NVG), iridocorneal endothelial syndrome (ICE) syndrome and extensive conjunctival scarring after retinal detachment surgery.

The following data were collected for each eye pre-operatively: name, age, gender, glaucoma diagnosis and lens status. The visual acuity, IOP, number of pressure-lowering medications were recorded both pre and post operatively. The intraoperative and post-operative complications were also noted. Successful IOP control was defined by Goldmann tonometry readings between 5 and 20 mm Hg.

SURGICAL TECHNIQUE

A 350 mm² Aurolab Aqueous Drainage Implant (AADI; Aurolab, Madurai, India) was used for the procedure. The surgery was performed under peribulbar anaesthesia using a mixture of 1% Lignocaine and 0.5% Bupivacaine. A fornix-based conjunctival peritomy was created spanning 4 - 5 clock hours in the supratemporal quadrant. The Tenon’s capsule was dissected by blunt dissection to expose the underlying sclera and dissection was carried out till the equator. The superior and lateral recti muscles were sequentially isolated, and the lateral expansions of the AADI device was placed beneath adjacent muscle bellies. The plate of the implant was then anchored to the sclera 9 to 10 mm
posterior to the limbus using two interrupted sutures of 8-0 nylon (monofilament polyamide black, Ethilon; Ethicon, Johnson & Johnson, India) through the fixation holes. After priming the implant using balanced salt solution, the tube of AADI was occluded tightly near tube plate junction using two 6-0 vicryl sutures (Braided-coated polyglactin 910 violet, Ethicon, Johnson & Johnson, India). The absence of flow through the tube was confirmed by irrigation of balanced salt solution into the tube via a 27-gauge cannula. The tube was then trimmed in a bevel-up fashion to have an intraocular segment of approximately 4 mm. A rectangular scleral flap with dimensions 4 x 4 mm was made and raised. Based on the intended site of implantation, using an ab interno approach, a 21 G vein needle (Infusion set-Type 500, JMS Singapore Pte Ltd) was used to make an entry into the anterior chamber thorough the opposite limbus. The needle was directed to the sulcus by crossing the pupil entering the plane under the iris thereby, emerging out through the bed of the scleral flap 2 to 2.5 mm from limbus tunnel partially. The anterior chamber was well formed using highly cohesive viscoelastic throughout the procedure. Through the exposed hollow end of the bevel of the needle (diameter - 800 microns), the tube (external diameter - 640 microns) was then inserted so as to be accommodated into the hollow bevel and was guided into the sulcus by withdrawing the needle along the direction of its insertion. The scleral flap was sutured with four 8-0 vicryl sutures (Braided-coated polyglactin 910 violet, Ethicon, Johnson & Johnson, India). The conjunctiva was then closed with the same 8-0 vicryl suture (Braided-coated polyglactin 910 violet, Ethicon, Johnson & Johnson, India) in a continuous fashion. Phacoemulsification was carried out as indicated after securing the plate via a temporal clear corneal section. A foldable PCIOL was implanted in the bag and the section was sutured with 10-0 nylon (monofilament polyamide black, Ethilon; Ethicon, Johnson & Johnson, India).
RESULTS

Nine eyes of nine patients of mean age 57.22 ± 7.85 years; (range, 45–66) who underwent the new surgical procedure within the study period met the entry criteria and were included. The mean follow-up period was 3.90 ± 0.97 months (range 3.07–6.17) and the male: female ratio was 7:2.

The pre-op and post-op parameters are as described in Table 1. Six of nine patients (66%) had secondary glaucoma namely neovascular glaucoma (50%), ICE syndrome, glaucoma post retinal detachment surgery and pseudoexfoliation glaucoma in 1 patient each (16%). Primary glaucomas (1 POAG and 2 PACG eyes) were seen in 3 of 9 patients (33%) respectively. Five of nine (55%) patients were pseudophakic and hence underwent primary AADI implantation. Four of nine patients (44%) had cataract and underwent phacoemulsification with intraocular lens implantation combined with primary AADI implantation.
### Table 1

<table>
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<th>Case number</th>
<th>Age (Years)</th>
<th>Gender</th>
<th>Glaucoma Diagnosis</th>
<th>Preoperative lens status</th>
<th>Preoperative IOP (mm Hg)</th>
<th>No: preoperative AGM</th>
<th>Surgical procedure</th>
<th>Postoperative IOP at 3 months (mm Hg)</th>
<th>No: Postoperative AGM</th>
<th>Complication</th>
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<td>NVG</td>
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<td>4</td>
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<td>ICE syndrome</td>
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<tr>
<td></td>
<td>6</td>
<td>6</td>
<td>F</td>
<td>PAC</td>
<td>Pseudophakia</td>
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<td>2</td>
<td>AADI implantation</td>
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<td>nil</td>
</tr>
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<tr>
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<td>M</td>
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<td>9</td>
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<td>AADI implantation</td>
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</table>


The IOP was reduced from a preoperative mean of 28.2 ± 9.80 mm Hg to a postoperative mean of 11.56 ± 2.65 mm Hg (p = 0.001). The mean number of preoperative medications for IOP control was reduced from 3.0 ± 0.7 to 0.4 ± 0.9 (p < 0.05) at the end of the follow-
up period. No significant improvement in visual acuity was noted from a median pre-operative log MAR of 0.60 (IQR 0.30 to 1.30) to a median log MAR of 0.48 (IQR 0.30 to 1.00) at the last follow-up visit.

There were no intraoperative complications. Post operatively, two patients (22%) had choroidal detachments. Although patient 9 subsided with conservative management, patient 4 needed anterior chamber reformation with peripheral anterior synechiae release and tube repositioning in view of post operative shallow chamber.

DISCUSSION

Tube shunt implantation into the posterior chamber sulcus may minimise adverse effects of anterior chamber placement thus, preventing complications associated with surgical vitrectomy during pars-plana insertion. Studies have shown comparable outcomes between sulcus placement and anterior chamber placement of the tube with a higher IOP reduction ratio in the sulcus group.13

To the best of our knowledge, this is the first case series describing this technique of tube shunt placement guided by a 21 G vein needle. The common technique of sulcus implantation was as described by Wiener and colleagues 12 involving Baerveldt (350 mm2) tube shunt placement. Following creation of a scleral tunnel and using a 23 G needle mounted on a Viscoat syringe, an entry was made and needle was directed towards the ciliary sulcus 1.5 to 2 mm from the limbus. The tube was then inserted through the tunnel and advanced until it emerged behind the iris. Sectoral iridectomy was additionally performed in non dilating pupils. Similarly, Tello et al 9 in their study of 8 eyes described ciliary sulcus insertion of the Barveldt tube shunt through a track created by a 23 G needle 2.5 mm from the limbus. The tube was then placed through the entry of the needle parallel to the posterior iris into the ciliary sulcus following insertion of Sodium
hyaluronate (Healon, Advanced Medical Optics, Santa Ana, California, USA) via a temporal paracentesis.

In contrast to these techniques, the main advantage of our ab interno procedure is the accuracy of tube placement in the sulcus in a controlled fashion by withdrawal of the needle. The ease of tube insertion may help shorten the learning curve and enable training surgeons to attain accurate tube placement in the sulcus, thus obviating the need for multiple entry attempts. Possible complications from this technique could be attributed to the large needle size for which, a generous fill of the anterior chamber and sulcus with a highly cohesive viscoelastic is recommended. In our procedure, obtaining the outer diameter specifications of the tube from the manufacturers and procuring a needle of adequate diameter ensured a reasonable fit. The specific 21 G vein needle from the IV set differed from a regular 21 G needle by having a shorter, less sharp bevel thereby limiting damage to the tube.

In the present case series, there were no patients with hyphema or significant postoperative inflammation suggesting minimal damage to the angle structures and limited contact of the tube to the iris pigment epithelium with this technique. Significant decrease in IOP and number of AGM was noted in our study similar to others. However, owing to the short follow-up period, the success rates per se could not be ascertained. The occurrence of choroidal detachments in two patients with the need for reoperation in one could be attributed to the angle closure glaucoma rather than peritubular leakage. Further studies comparing both the methods of tube insertion would be helpful in ascertaining the same.

The limitations to this study is its retrospective nature, small sample size, limited follow-up and lack of corneal endothelial counts prior to the procedure. Using a hollow needle of adequate diameter, this technique is amenable for use with other glaucoma drainage devices as most of them have a silicone tube of identical dimensions to the AADI implant.
The effectiveness of this implantation technique could also be better substantiated if compared with the conventional method.

CONCLUSION

Our technique of sulcus placement of the AADI tube is a precise and simple technique of tube insertion. It is a safe alternative to existing procedures limiting multiple blind entries and thereby, preventing damage to adjacent angle structures. Further study is required to validate the long-term safety and efficacy of this technique.

REFERENCES


Figure 1: Needle exiting the scleral bed partially 2.5 mm from the limbus
Deciphering The Conundrum Of Aerosolisation During Non-Contact Tonometry (NCT)

Dr. Nikhil Balakrishnan

PURPOSE:

To study the proclivity of aerosol generation during NCT & its impact during the COVID-19 pandemic

METHODS:

NCT was performed on human eyes under Normal settings, with a single drop & 2 drops of lubricant. Aerosols & droplet generation was imaged using high speed Shadowgraphy & frontal lighting techniques.

RESULTS:

In natural settings there was no splash or aerosol production. A single small droplet of around 470ì was observed being ejected from the tear film when 1 drop of lubricant was
used prior to NCT, the trajectory of which was then computed. When 2 drops of lubricant were used, we noted copious amount of tear ejection in the form a sheet which broke up into multiple small droplets which traversed back to the tonometer

CONCLUSION:

There was no visible aerosol generation during NCT performed in natural settings & is thus safe to perform even in the COVID era. NCT is best avoided in conditions with high tear volume (natural or artificial) as it would lead to droplet spread & tactile contamination.

INTRODUCTION

The World Health Organization (WHO) declared COVID-19 as a "Public Health Emergency of International Concern" in late January.¹ The pandemic is escalating at an alarming rate despite numerous outbreak control measures.² The transmission of the novel coronavirus (2019-nCoV) occurs predominantly through direct contact³ or via droplets when an infected individual coughs or sneezes.⁴ Medical staff are at high risk as social distancing is difficult to maintain amidst their work environment and several patients may be asymptomatic.⁵ While it is easier to safeguard against contact based infection, aerosols and droplets generated during diagnostic and surgical procedures pose a concern to healthcare workers since they may become airborne and not easy to track. Precise measurement of intraocular pressure (IOP) via tonometry is an essential practice in an ophthalmology clinic.⁶-⁷ The ideal device must be easy to use, fast, safe and precise, irrespective of patient posture, age, patient compliance and operator bias.⁸ The Goldmann applanation tonometry (GAT) is a widely used method for measuring IOP.⁹-¹⁰ However, noncontact tonometer (NCT) (air-puff tonometry) is also used widely. It uses an air-puff to flatten the cornea. This method has advantages since no topical anaesthetic or risk of corneal abrasion is involved.¹¹
There is some evidence of tear film dehiscence and aerosol formation during NCT. The SARS-CoV-2 virus may reside in the tears and conjunctival secretions of symptomatic COVID-19 patients. Hence, there is concern regarding the usage of NCT during the COVID-19 pandemic. Based on their size, droplets can be sub grouped as large (> 10-20 μm) and small (< 10-20 μm) droplets. The larger droplets don’t remain suspended in air, settle quickly and hence don’t get deposited in the lower respiratory tract. By definition, aerosols are suspensions in air (or in a gas) of solid or liquid particles and small enough to remain suspended in air due to low settling velocity. Many studies have a size cut-off of < 5 μm for aerosols. Particles with diameter lesser than 3 μm don’t usually settle. Most particles of size > 6 μm can get trapped in the upper respiratory tract. To quantify aerosols and droplets, shadowgraphy is a visualisation technique in which the object to be imaged is inserted between the light source and the camera. Due to the density difference between the medium (air) and object (aerosol and droplet), light rays naturally bend and create a shadow which defines the boundary of the object. Shadowgraphy is a preferred technique for high speed imaging where the sensitivity is low at high frame rates. We have previously used this technique to quantify the spread of aerosols and droplets during phacoemulsification and flap cut with a microkeratome. Both the studies revealed generation of droplets of large sizes which had minimal risk of aerosolization. Frontal lighting is another imaging technique where in light is directly shone upon the device to be imaged. Therefore, the aim of this study was to quantify the spread of aerosol and droplet generation during NCT using shadowgraphy and frontal imaging.

METHODOLOGY

This experimental study was approved by the institutional research and ethics committee of Narayana Nethralaya Multispecialty Hospital, Bangalore, India and conducted in accordance with the tenets of the Declaration of Helsinki. The study was performed in collaboration with the Department of Mechanical Engineering of the Indian Institute of
Science, Bangalore, India. First, NCT was performed on one eye of each subject under normal settings (no eye drop instilled before NCT). Then, NCT was repeated immediately after instillation of a single drop of a lubricant (Systane Ultra lubricant eye drop, Alcon Laboratories, Fort Worth, TX). NCT was again repeated immediately after the instillation of two drops of lubricant. A ten-minute interval was maintained between each NCT measurement. The above process was repeated in 6 subjects who volunteered for the study. The Shin-Nippon NCT-200 (Rexam Co. Ltd., Osaka, Japan) was used for the experiments.21

The shadowgraphy technique involved the use of a high-speed camera, the Mini-UX100 (Photron USA Inc., San Diego, USA) coupled with a macro lens (ATX 100, 100 mm, f2.8D; Kenko Tokina Co., Ltd., Tokyo, Japan) for imaging. The resolution of the camera was 1280 × 1024 pixels. The aperture was set to f / 32 for a maximum depth of field. The continuous illumination used a high-power LED source (Constellation 120, Veritas) which was positioned opposite to the camera. The NCT device was placed between the light and the camera for high-speed shadowgraphy (side lighting setup in Figures 1A and B). The camera was manually triggered to acquire images before the NCT was triggered. For the frontal lighting setup of shadowgraphy, the illumination was placed in front of the NCT device so that the light fell directly on it (Figure 1C). The light emitting diode (LED) light source was placed behind the camera to image the tear droplets distinctly (Figure 1D) since the normal morphology of the human face, location of the eyes and tilt of the human head sometimes impeded the shadowgraphy technique. By placing a white tape on the subject's nose, enough backlighting was possible to make the cornea appear like a shadow which allowed sharper imaging of the indentation of the cornea during applanation.

For the fluorescein dye analyses, we stained the conjunctiva of the volunteers with a sterile ophthalmic fluorescein sodium strip (Fluro Strips, Contacare Ophthalmics & Diagnostics, Vadodara, India) after moistening the tip with a lubricant drop and 1 mg of
Figure 1: Experimental Set Up

[A] Shadowgraphy setup with high speed camera and light emitting diode (LED) opposite to one another with object to be imaged in between. [B] Shadowgraphy setup with subject. [C] Frontal lighting setup with LED light source placed behind the camera. [D] Frontal lighting setup with subject. [E] Fluorescein analysis setup with a blue LED light and a bandpass filter attached to the camera. [F] Fluorescein analysis setup with subject.
sodium fluorescein. The volunteers were requested to blink repeatedly following a period of eye closure after the application of the strips. Then, tonometry was performed. The fluorescein absorbed wavelengths between 460 and 480 nm and emitted fluorescence in the range of 530 to 560 nm. To capture these emissions from the illuminated eye, we used a 30 W blue LED as an excitation source (450 nm) and imaged with a bandpass filter (527 nm) placed on the camera. We used 3 different cameras for the fluorescein dye analyses. Firstly, we used a 16 megapixel smart phone camera (Realme 3 Pro - Realme Mobile Telecommunications Private Limited, Haryana, India) for external video filming in a darkly lit room. Videos were captured in 4K resolution and at 30 frames per second (fps). Secondly, a Nikon D7200 digital single-lens reflex (DSLR) camera was used to capture high resolution images (24 megapixels) at a shutter speed of 2.5 seconds. Videos on the same camera were acquired at 25 fps. Thirdly, the Mini UX100 was used at low acquisition rate (50 fps) to check for aerosol and droplet generation. The lens used for all the experiments was the ATX Pro 100. Figures 1E and F show the fluorescein setup.

A simple one-dimensional analysis of the aerosol and droplet spread was performed similar to our earlier work. Assume that a droplet of diameter (D µm) was ejected with a velocity ud (horizontal component) during the course of an air puff tonometry. Our out-patient departments (OPD’s) do not have controlled air-conditioning and a natural air velocity (uair) ~ 0.1 to 0.2 m/sec in the room was considered assuming that the room was closed from inside. However, the presence of an air-conditioning unit or a table fan can enhance uair to as much as 1 m/s. The appropriate governing drag equation for the droplet can be written as:

\[
\frac{du_d}{dt} = \frac{18 \mu_f u_{rel} (u_{air} - u_d)}{r^2 \rho_d u_{rel}} \quad [1]
\]
where, \( u_{rel} = \sqrt{(u_{air} - u_d)^2 + v_d^2} \), \( u_d = r \times \text{settling rate of droplet,} \) \( \mu_f \) was the viscosity of air, \( \rho_f \) was the density of air, \( \rho_d \) was the density of droplet and \( g \) was the acceleration due to gravity. The droplet evaporates as well as settles due to gravity simultaneously. The evaporation timescale can be estimated from the \( D^2 \) law 1 while the appropriate settling rate \( (v_d \text{ in m/sec}) \) was estimated from the Stokes equation:

\[
v_d = \left( \frac{\rho_d - \rho_f}{18 \mu_f} \right) g \frac{D^2}{\rho_d \rho_f g D} \quad [2]
\]

The calculation assumed that the human eye was positioned approximately 50 cm from the table on which the NCT was placed. Thus, the timescale of droplet settling can be obtained from equation 2 as follows:

\[
t_s = \frac{1}{v_d} = \frac{18 \mu_f}{\rho_d - \rho_f g D} \quad [3]
\]

The final horizontal distance \( (x) \) travelled by the droplet was determined from the smaller of the two quantities, the evaporation time scale and settling time scale. Additional details about the properties of air and droplet used for these calculations were provided in our earlier study. The droplet sizes were measured using custom algorithms as described in our previous studies.\(^{19,20}\)

RESULTS

Unlike our previous studies shadowgraphy was difficult to perform as the anatomy of the human face and the setting of the human eye obstructed distinct imaging of the cornea and conjunctival surfaces. The cornea appeared as a thin white film and deformed upon impact of the air puff. Figures 2A to E show a sequence of frames captured with shadowgraphy. Some deformation was evident in Figure 2C. After applying one drop of lubricant, a large droplet of diameter \( \sim 470 \mu m \) was observed originating from the eye (Figure 2E). On superimposition of the sequential images, we could chart the trajectory of the same
[A] Human cornea prior to applanation (t=0 seconds). [B] Impingement of the air puff leading to sliding down of the tear film and subsequent formation of a bulge near the lower lid (t=3 milliseconds). [C] Maximum applanation (deformation) of the cornea (t=11 milliseconds). [D] Cornea regaining its original shape (t=14.5 milliseconds). [E] Ejection of a single droplet ~470 µm from the lower fornix formed from the displaced tear film (t=28.5 milliseconds). [F] The trajectory of the ejected tear droplet illustrated by superimposition of sequential frames. The scale bar in black equals 5 mm while the one in grey equals 2.5 mm.

(Figure 2F). To overcome the shortfalls of shadowgraphy imaging, we repeated the measurements using frontal lighting. The images were acquired at a rate of 2000 fps and shutter speed of 1/20000s. We first imaged without the instillation of any eye drop. We observed the presence of a tear film with minimal pooling of tears in the lower meniscus prior to NCT. No formation of any droplet or aerosol was observed during the procedure (Figure 3). On instillation of a drop of lubricant, we witnessed pooling of fluid in the lower meniscus, along with tear drops on the lower eyelashes prior to tonometry (Figure 4). Impingement of the air puff caused deformation of the cornea which caused the fluid film on the ocular surface to be displaced. In one instance, ejection of a tear drop was noted which traversed towards the lashes of the upper lid. The drop was seen as suspended from the upper lashes
[A] Human cornea prior to applanation (t=0 seconds). [B] Impingement of the air puff leading to deformation of the cornea (t=34 milliseconds). [C] Cornea regaining its normal shape following maximum deformation (t=44 milliseconds). [D] Cornea returned to its original shape (t=56 milliseconds). No droplets noted during any frames. The scale bar in black equals 5 mm.

Figure 3: Frontal lighting imaging in normal eye condition
(Rate - 2000 frames per second (fps) and shutter speed 1/20000 s)

[A] Human Cornea prior to applanation (t=0 seconds). Droplets noted on lower eyelashes. [B] Impingement of the air puff leading to deformation of the cornea (t=14 milliseconds). Minimal movement of the droplets on the eyelashes noted. [C] Corneal deformation (t=24 milliseconds). Droplet being ejected from the cornea travelling upwards towards the upper eyelashes. [D] Cornea returned to its original shape (t=56 milliseconds). Ejected droplet observed trapped on the upper eyelashes.

Figure 4: Frontal lighting imaging in eye instilled with one drop of lubricant
(Rate - 2000 fps and shutter speed 1/20000 s)
following return of the cornea to its normal state (Figures 4C and D). In another instance following corneal deformation, the fluid from the lower meniscus moved along the meniscus laterally up to the lateral canthus of the eye and was evidently imaged (indicate by white circle in Figure 5). On repeating the test for a third time, we observed break-up of the fluid film and ejection of two droplets (Figure 6).

On instillation of two drops of lubricant, there was excessive fluid in the lower meniscus of the eye along with presence or droplets in the lower lashes (Figure 7). On impingement of the air puff and after corneal deformation, the tear film was pushed away from the ocular surface. A sheet of fluid was initially noted which disintegrated into droplets (Figure 7). The diameters of these droplets were found to be in the range of 100 to 500 μm among all subjects (Figure 7). In all the subjects, we noted that the droplets originated from the fluid lake along the lower lid margin. On air impingement, a redirection of air impulses from the centre of the cornea towards the conjunctival fornices occurred that led to separation of eyelid margin from the sclera. If pooling in the lower fornices was present, NCT caused an excursion of fluid. Since the smallest detectable droplet diameter was ~100 μm, the process was controlled primarily by the settling timescale. To compute the distance traversed by these droplets, we used the drag equation 1 taking into consideration two settings of room air velocity, ~0.1 m/s and 1 m/s. Figure 8 shows the estimated distance traversed by the droplets as a function of diameter. This distance would be traversed by the droplet if left unobstructed. The initial value of droplet’s horizontal velocity (ud) was calculated as 1 m/sec from the sequential images shown in Figure 7. The distance between the point of contact of the human eye and the pneumatic port of the tonometer was approximately 11mm. Hence, droplets smaller than 300 μm can settle on the device even in case of low velocity of 0.1 m/sec (red circles in Figure 8). The spread distance increased with greater air velocity of 1 m/sec (blue circles in Figure 8). The simple calculation presented here does not account for the clustering effect observed in sprays.
[A] Human Cornea prior to applanation (t=0 seconds). [B] During air impingement droplet noted near the lower lid at the lower meniscus (t=8 milliseconds). [C] Movement of the droplet along the lower lid towards the lateral canthus (t=20 milliseconds). [D] Further movement of droplet towards the lateral canthus (t=28 milliseconds). The scale bar in grey equals 5 mm.

Figure 5: Frontal lighting imaging in eye instilled with one drop of lubricant (Rate - 2000 fps and shutter speed 1/20000 s). Cornea observed blur as plane of focus is on the lateral bulbar conjunctiva.

[A] Human cornea prior to applanation (t=0 seconds). [B] During air impingement minimal deformation of the cornea noted (t=10 milliseconds). [C] Ejection of droplets from the cornea (t=26 milliseconds). [D] Ejected droplets traversing towards the pneumatic port of the Non-contact tonometer (t=68 milliseconds). The scale bar in grey equals 5 mm.

Figure 6: Frontal lighting imaging in eye instilled with one drop of lubricant (Rate - 2000 fps and shutter speed 1/25600 s).
[A] Human cornea prior to applanation (t=0 seconds). [B] During air impingement deformation of the cornea noted (t=12 milliseconds). Ejection of droplets from the lower meniscus appear like a sheet which break into droplets lower in the frame. [C] Maximum applanation (deformation) of the cornea (t=26 milliseconds). [D] Superimposition of sequence of images showing profuse droplet generation. The scale bar in grey equals 5 mm.

Figure 7: Frontal lighting imaging in eye instilled with two drops of lubricant (Rate - 2000 fps and shutter speed 1/25600 s).

Figure 8: Mathematical modelling to compute the maximum distance traversed by a droplet if the NCT procedure was carried out in either a room with low airflow or in an air conditioned room.
The fluorescein experiments confirmed the observations our frontal imaging experiments. No aerosol production in a natural eye setting (Figure 9A) (without the instillation of eye drop) was seen on either smartphone imaging (Figure 9B), DSLR camera (Figure 9C), or high-speed imaging (Figure 9D).

Figure 9: Fluorescein analysis in normal human eye conditions. Different cameras used for imaging were 16 megapixel smartphone camera using nightscape ultra HD Mode at 30fps. 24 megapixel Nikon D7200 DSLR camera shutter at 25fps with shutter speed of 2.5 seconds. Mini UX100 at 50fps with ATX Pro 100 lens.

When one drop of lubricant was instilled, we noted supplementary volume of fluid in the lower fornix (Figure 10A) and minimal aerosol production on tonometry. The smartphone(Figure 10B) and DSLR camera(Figure 10C) picked up droplets being emitted from the ocular surface on air impingement, which appeared to settle on the nose bridge of the subject. High speed photography revealed emission of droplets from the lower tear meniscus which were emitted initially as a sheet and subsequently disintegrated (Figure 10D).

[A] Normal eye conditions captured on the nightscape mode of a smartphone. Minimal tear film meniscus is noted near the lower lid. [B] No ejection of any droplets noted on Non-contact tonometry. Video captured in 4k in nightscape mode of a smartphone. [C] Images captured on Nikon DSLR. No generation of any aerosols noted [D] No production of aerosols captured by Ultra High resolution Mini UX 100 camera.
When two drops of lubricant eye drop were instilled, we observed pooling of fluorescein stained tears in the lower fornix with some spillage towards the medial and lateral canthi (Figure 11A). Via the nightscape smartphone videography, there was generation of droplets (Figure 11B and C), which traversed back up to the NCT contaminating it (Figure 11D and E). The DSLR (Figure 11F and G) and high-speed imaging (Figure 11H and I) too demonstrated ample dispersion of droplets. Droplet size and trajectory in fluorescein analysis could not be computed because of the halo around the droplets obtained and the low speed (50 fps) of acquisition respectively.
DISCUSSION

The fact that aerosols and large droplets can transmit viruses is well known.\textsuperscript{17} Hence, the transmission of COVID-19 could occur through respiratory droplets.\textsuperscript{2,3,4,5} Thus, the mucosa (mouth or nose) or conjunctiva are at risk of being exposed to the infected respiratory droplets. Another mode of transmission of the COVID-19 virus was through fomites in the environment around the infected person.\textsuperscript{6} Airborne transmission differed from droplet transmission as it denoted the presence of aerosols that were smaller than 5μm in diameter. These have the potential of surviving in air for longer periods of time and also travel greater
distances. Thus the air or the objects around a potentially infected person may be a potential source of infection. Hence, the procedures or treatment modalities that generate aerosols could result in airborne transmission of COVID-19.

Recommendations from physician bodies indicated that NCT should be avoided. Some bodies suggested the use of single use disposable tonometer tips as cleaning of the tips with 70% alcohol weren’t effective in disinfecting tips infested with the SARS-CoV-2 virus. Due to these guidelines, many eye clinics may have discontinued the use of NCT and moved on to contact tonometry. The goal of this study was to precisely determine if there was risk of aerosolization from NCT procedure. We observed no aerosolization from the eye of the subjects without the instillation of eye drop. This was a critical finding. On instillation of a single lubricant drop, we observed accumulation of fluid in the lower fornix. On air impingement, dispersion of this fluid was observed. Most of the fluid was either drained along the lower meniscus into the lake near the lateral canthus or a small amount of fluid was ejected in the form of droplets. However, these droplets only travelled up to the lashes and weren’t emitted outside the eye. Only in one of the subjects did we observe droplets being ejected which traversed back up to the pneumatic port of the tonometer. This could possibly be a source of infection if the infected patients had ocular symptoms of COVID-19. The pneumatic port once infected may act as a reservoir for the virus and could transmit the same to the successive patients undergoing tonometry. In our final set of experiments, instilling two drops of lubricant resulted in significant splatter of fluid from the ocular surface. These drops may not only stay suspended in the air for long periods of time because of their size but also may contaminate the surfaces on which they land.

As long as the eye was in its natural condition, performing NCT would be safe. However, the dispersion of droplets from the ocular surface could be a potential source of infection in cases of epiphora. Hence, NCT should be avoided in such patients, e.g., allergies, meibomian gland disorders, dry eyes. Since epiphora is common after
phacoemulsification\textsuperscript{11}, pterygium surgery\textsuperscript{12}, refractive surgery\textsuperscript{13}, lacrimal apparatus surgery\textsuperscript{14}, squint correction\textsuperscript{15} and trabeculectomy\textsuperscript{16}, NCT should not be performed immediately after the surgery. The use of a protective shield on ophthalmic equipment such as slit lamps, optical coherence tomography (OCT) and fundus cameras was recommended.\textsuperscript{17} However, the use of the same on a tonometer would not be effective as placing of a shield between the pneumatic port and the eye would prevent the air puff from reaching the eye. To our best knowledge, only one previous study evaluated the dispersion of aerosols during NCT. Britt et al. used fluorescence photographic technique to study the presence of aerosols.\textsuperscript{12} A major drawback of this method was the inability to gauge the size of the aerosols, chart their trajectory and spread. Contrary to our findings, they reported the dispersion of aerosols and droplets on NCT in most eyes.\textsuperscript{12} This could be explained by the fact that they used a drop of fluorescein to stain the ocular surface in every subject. Hence, we used a moistened fluorescein strip instead of fluorescein drops in all subjects to replicate the state of the normal human eye. The observation of excessive splatter on addition of a drop of methylcellulose was akin to our findings.\textsuperscript{12}

They also used two different NCT's, the American Optical (AO) NCT II (Cambridge Instruments Inc, Cambridge, Mass) and Keeler Pulsair (Keeler Instruments Inc, Broomall, Pa) tonometer. The AO NCT used a piston generated air impulse that linearly increased over the first 8 milliseconds after which it progressively decayed. The Keeler Pulsair used an electrical pump to create a pressure gradient and a ramped air impulse for applanation. It consisted of a sub-30 mm and a supra-30 mm mode based on the IOP of the patient. The Supra-30mm mode created a more forceful impulse which in turn would lead to more splatter. In comparison to this, we used the Shin Nippon-200 NCT which used a newly developed Smart Puffing Controlled system. This system had an integrated algorithm so as to adjust air-puff pressure instantly based on the patients IOP.\textsuperscript{21} Although we did not use an adjustable triggering device for the synchronization of the camera (for shadowgraphy and frontal imaging) with the tonometer, we tweaked the frame per seconds
rate of the cameras so as to ensure that we capture the entire video of the air puff indenting the cornea up until the droplets being emitted.

By using three different imaging set-ups (shadowgraphy, frontal lighting and fluorescein), we were able to image the fluid dynamics of splatter from the eye during NCT.

It is important to note the stochastic nature of droplet creation from the fluid splatter. Atomization of the fluid depends on several factors, e.g., air-puff pressure, duration of air-puff, thermo-physical properties of the fluid, angle of inclination of the eye to the puff. Nonetheless, our experiments showed that the droplet diameters were bounded up to 500 μm (Figure 8) in all the captured frames of the side lighting videos. For each eye, as many as 1000 frames were captured over a 2 second period. However, the distribution of the droplet sizes between the frames differed sharply due to the stochastic (random) nature of droplet creation in such experiments. This is a well-known phenomenon in the field of droplet fluid mechanics.\(^{18}\) Thus, assessing repeatability between frames or between the eyes was physically unrealistic. We evaluated nearly 8000 frames (8 eyes) and focused on the frames which yielded the smallest droplet diameter. Based on our detailed experiments, we concluded that NCT did not lead to droplet or aerosol generation, when the eye was in its natural state. However, any condition which could lead to watery eyes (natural or artificial) should be an exclusion criterion for performing NCT.

REFERENCES


23. M M, Sahu S. Analysis of droplet clustering in air-assist sprays using Voronoi
Raised Intraocular Pressure In Thyroid Associated Ophthalmopathy: Non-Responsiveness And Paradoxical Association With Glaucoma Progression

Dr. Karthikeyan Mahalingam

INTRODUCTION:

Grave's disease is an autoimmune disorder characterized by hyperthyroidism, thyroid associated ophthalmopathy (TAO) and dermatopathy wherein most patients are hyperthyroid.\cite{1,2} Patients with TAO present with eyelid erythema, conjunctival injection, eyelid retraction associated with exophthalmos or eyelid fibrosis.\cite{2} Increased orbital volume and fibrosis of extraocular muscles (EOM) may lead to bilateral exophthalmos, exposure keratitis, restriction of EOM movements, diplopia and compressive optic neuropathy.\cite{3} These patients also have raised intraocular pressure (IOP), first documented by Wesseley in 1918.\cite{4} It may be due to glycosaminoglycans accumulation in trabecular meshwork, increased episcleral venous and orbital pressure, responsiveness to steroids administered for TAO and restrictive myopathy (gaze related).\cite{5,6} Thyroid dysfunction and its treatment can also cause changes in IOP.\cite{7-11} The various options for management...
of raised IOP in TAO includes topical glaucoma medications, laser trabeculoplasty, glaucoma filtration surgery and treatment of TAO with steroids or orbital decompression. This raised IOP has poor response to medications which increase the aqueous outflow. Some patients may even have a paradoxical progression of the disease with IOP lowering. Inspite of high IOP, TAO patients have lesser tendency to glaucoma progression compared to general population. Maintaining optic nerve perfusion plays a major role in glaucoma progression. There is no standardized protocol for managing raised IOP in TAO. Most patients coming to glaucoma services are being treated like routine glaucoma patients without knowing the fact that decreasing IOP can also paradoxically lead to glaucoma progression. There is a paucity of studies in literature which assess the effect of orbital decompression on IOP in patients with TAO. We aim to assess the course of raised IOP in TAO patients i.e. response to routine glaucoma treatment, orbital decompression and also its association with glaucoma progression.

METHODS:

An ambispective observational study was conducted at the tertiary eye care centre in North India after obtaining institutes ethical committee clearance. TAO Patients visiting glaucoma services and fulfilling our criteria were recruited after obtaining consent.

INCLUSION CRITERIA:

Patients with thyroid associated ophthalmopathy defined by Otherwise unexplained eyelid retraction with lagophthalmos with or without other clinical signs of inflammation and with or without evidence of thyroid dysfunction (or) unexplained proptosis (Hertel e; 17 mm/2 mm interocular difference), extraocular muscle enlargement, orbital congestion, or inflammation accompanied by either eyelid retraction with lagophthalmos or evidence of thyroid dysfunction and untreated IOP > 21 mm Hg in two or more occasions measured by goldmann applanation tonometry in primary gaze.
EXCLUSION CRITERIA:

Patients with other forms of glaucoma like primary open or closed angle glaucoma, traumatic glaucoma, uveitic glaucoma etc. Patient not willing to give consent or follow up.

Parameters like age, sex, IOP, duration of follow up, proptosis, central corneal thickness, cup-disc ratio (CDR), type of treatment given and thyroid status were noted. Their past records were noted and patients were followed up prospectively. Data entry was done in Microsoft excel and SPSS version 23 was used for statistical analysis. The normal distribution of data was tested by the Kolmogorov-Smirnov test. Accordingly, continuous variables were reported with their mean ± standard deviation (SD) or median, interquartile range (IQR). Eyes were divided into groups depending upon the response to glaucoma management and variables were compared. Pearson Chi square test was used for categorical variable. Since both the eyes of the patient were taken for analysis, generalized estimating equation (GEE) method was used to correct the bias. A P-value of <0.05 was considered significant.

RESULTS:

42 eyes of 21 TAO patients with OHT were studied. The mean age of participants was 43.8 ± 11.7 years with similar sex ratio (male: female::1:1). Median duration of follow up was 30 months (IQR: 18 to 37). Baseline IOP was 28.1 ± 6.4 mm Hg, baseline CDR was 0.48 ± 0.16:1, CCT was 553.6 ± 31 µm, baseline Hertel’s measurement was 23.6 ± 3.9 mm. IOP of 15 eyes (35.7%) (9 patients) normalised with topical glaucoma medications. These eyes were labelled as responders. 23 eyes (13 patients) where IOP was either not controlled or required orbital decompression for IOP control were termed as non-responders. 4 eyes with with IOP < 25 mm Hg and no glaucomatous cupping or field defects were observed without glaucoma medications. The characteristics of responders
and non-responders are compared in Table 1. Six out of eight eyes (75%) which had undergone orbital decompression achieved IOP control. Three eyes underwent trabeculectomy with mitomycinC (MMC) out of which 2 needed orbital decompression. Two eyes underwent selective laser trabeculoplasty (SLT). Trabeculectomy and SLT were not helpful in IOP control. 20 eyes (47.6 %) of eyes had paradoxical corelation of IOP with glaucoma progression. Out of these 20 eyes, in 6 eyes glaucoma progressed despite controlled IOP and 14 eyes did not show progression with high IOP over a median follow up of 36 months (IQR 24 to 40).

Table 1:

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Responders (15 eyes)</th>
<th>Non-responders (23 eyes)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44.5 ± 12.7</td>
<td>41.7 ± 9.8</td>
<td>0.54*</td>
</tr>
<tr>
<td>Sex (Male: Female)</td>
<td>1:2</td>
<td>2.8:1</td>
<td>0.02#</td>
</tr>
<tr>
<td>Thyroid status:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthyroid</td>
<td>6 (40%)</td>
<td>14 (60.9%)</td>
<td>0.05#</td>
</tr>
<tr>
<td>Euthyroid</td>
<td>5 (33.3%)</td>
<td>1 (4.3%)</td>
<td></td>
</tr>
<tr>
<td>Hypothyroid</td>
<td>4 (26.7%)</td>
<td>8 (34.8%)</td>
<td></td>
</tr>
<tr>
<td>Baseline IOP (mmHg)</td>
<td>24.5 ± 5.1</td>
<td>30.8 ± 6.3</td>
<td>0.01*</td>
</tr>
<tr>
<td>Baseline CDR</td>
<td>0.42 ± 0.1 : 1</td>
<td>0.53 ± 0.1 : 1</td>
<td>0.76*</td>
</tr>
<tr>
<td>CCT (µm)</td>
<td>544.7 ± 21</td>
<td>560.8 ± 34</td>
<td>0.12*</td>
</tr>
<tr>
<td>Proptosis</td>
<td>9 (60%)</td>
<td>20 (87%)</td>
<td>0.006*</td>
</tr>
</tbody>
</table>

*Adjusted for presence of clustering by using Generalized Estimating Equation method, 
#Pearson Chi square test
DISCUSSION:

In our study, only one third of the eyes showed response to topical glaucoma medications. Majority of eyes had non-significant IOP reduction with multiple glaucoma medications, SLT or trabeculectomy with MMC. These non-responders showed significant male predominance and had significantly higher baseline IOP. Most of the non-responders were in either hyperthyroid or hypothyroid state. There are reports in literature suggesting that hypothyroidism can increase the IOP and treatment of hypothyroidism has been associated with control the IOP.\cite{10,11} Presence of proptosis was significantly higher in non-responders.

According to Cockerham et al, the prevalence of raised IOP in TAO patients was 24%, which was very high compared to general population (approximately 5%).\cite{14,16} The progression of ocular hypertension to glaucoma was less than 2% in TAO patients. This was less compared to general population with ocular hypertension which had 6.7% to 17.4% progression rate over 5 years (3.5% per year).\cite{17,18} In our study 14 eyes with raised IOP did not show progression of glaucoma. The plausible reasoning for this could be simultaneous increase in intraorbital pressure, which helps maintain optic nerve head perfusion.

In our study, 6 eyes showed glaucoma progression despite achieving target IOP. An indirect estimator of intraorbital pressure is venous outflow pressure (VOP).\cite{13} It is believed that VOP must be < 5 mm Hg higher than IOP in order to maintain ocular perfusion pressure whereas a difference above that, can cause compromised perfusion leading to development of scotomas despite an actual lowering of IOP.\cite{13} Thus ophthalmodynamometry for assessment of VOP is helpful in patients who show signs of glaucomatous progression. Even if IOP is high but the difference with VOP is < 5 mm Hg, IOP may not require lowering despite the high values seen.
Since the primary pathology in TAO, is raised intraorbital pressure, raised IOP is often refractory to medical management or glaucoma filtration surgeries. In our study, 75% of eyes (6 out of 8) eyes achieved target IOP after orbital decompression. In a study by Kalmann et al orbital decompression was performed in 5 TAO eyes with raised IOP and IOP was reduced in all eyes post-operatively.\[5\] Onaran et al showed that combined orbital bone and fat decompression in 72 eyes with TAO significantly decreased IOP and increased the superior ophthalmic vein blood flow velocity.\[19\] Thus addressing the elevated episcleral venous pressure by orbital decompression would be helpful in reducing the IOP in patients with TAO.\[5,13,19\]

CONCLUSION:

Risk factors for poor response to glaucoma therapy in TAO patients include male gender, higher baseline IOP, uncontrolled thyroid state and proptosis. If indicated, orbital decompression should be considered before planning for any glaucoma surgery. Maintaining the optic disc perfusion by keeping the balance between intraorbital pressure/VOP and IOP is required rather than reducing IOP in all cases. As measurement of VOP is not practically possible in all cases, stringent IOP reduction should not be considered unless glaucoma progression occurs (figure).
REFERENCE:


Outcomes Of Inferior Turbinate Tarsal Infracture For Congenital Nasolacrimal Duct Obstruction

Dr. Gaurav Garg

ABSTRACT:

PURPOSE:

Probing and inferior turbinate tarsal infracture in congenital nasolacrimal duct obstruction have been reported with variable success. There is a lack of literature with nasal endoscopic guided inferior turbinate tarsal infracture. To determine the efficacy and safety of inferior turbinate tarsal infracture in cases of congenital nasolacrimal duct obstruction complicated by the impaction of the inferior turbinate.

METHODS:

It was a retrospective, non-randomized, non-comparative, interventional case series conducted in a tertiary referral eye centre in 69 eyes of 55 children from July 1st, 2013 to Sep 30th, 2019. Lacrimal probing combined with nasal endoscopy-guided inferior turbinate tarsal infracture was done. The resolution of congenital nasolacrimal duct obstruction at 3 months was the primary outcome measure.
RESULTS:
The mean age at presentation was 29.1 ± 15.3 months with a mean duration of symptoms of 27.4 ± 15.8 months. The mean follow-up was 44.9 ± 23.8 months. The results were gratifying with the resolution of congenital nasolacrimal duct obstruction in 98.4 % (n = 62 / 63) and one needed a repeat of infracture. 6 children also had an atonic sac that resolved in 2 with just Crigler massage, 3 required dacryocystorhinostomy on subsequent follow-up, and 1 developed lacrimal abscess which was managed by incision and drainage.

CONCLUSION:
Nasal endoscopy-guided inferior turbinate tarsal infracture is highly effective and safe, with an impressive resolution of congenital nasolacrimal duct obstruction. Thereby, this study provides an insight into non-dacryocystorhinostomy methods to tackle congenital nasolacrimal duct obstruction.

KEYWORDS:
Syringing and probing; Lacrimal probing; Inferior turbinate impaction; Inferior turbinate infracture; Congenital nasolacrimal duct obstruction; nasolacrimal duct obstruction.

KEY MESSAGES:
Herein, we describe children with congenital nasolacrimal duct obstruction who were diagnosed with inferior turbinate impaction on nasal endoscopy. It was overcoming by inferior turbinate tarsal infracture with an excellent success rate.

ABBREVIATIONS:
CNLDO: Congenital Nasolacrimal Duct Obstruction; DCR: Dacryocystorhinostomy; TMH: Tear Film Meniscus Height; FDDT: Fluorescein Dye Disappearance Test; N/A - Information not Available or Applicable
INTRODUCTION:

Congenital epiphora affects almost 20% of the newborns with more than 90% resolving spontaneously in their infancy without any intervention and more than 60% of the remaining in the following year. The remaining are diagnosed as congenital nasolacrimal duct obstruction (CNLDO). Usually, obstruction or failure of canalization of the distal end of the nasolacrimal duct causes CNLDO, though it can also rarely occur due to the other obstructed parts of the lacrimal drainage system (LDS). This may necessitate surgical intervention in the presence of symptoms. Most commonly these children present as mild to severe epiphora with may be associated with either mucoid, purulent discharge, or mucocele. To manage the CNLDO, there are various treatment options: Crigler massage, probing, irrigation by syringing, silicone tube intubation, inferior turbinate tarsal infracture, balloon dacryoplasty, dacryocystorhinostomy (DCR). The choice of intervention depends upon the etiology and complexity of the case.

The most common cause of CNLDO is the membrane over the valve of Hasner which either resolves spontaneously or may require probing. CNLDO can also present as bony obstruction due to fusion or close opposition between the inferior turbinate and lateral wall of the nasal cavity with non-development of inferior meatus or inferior nasolacrimal duct. This can be treated by medialization of inferior turbinate towards the septum of the nasal cavity with the help of the blunt end of the freer elevator.

Literature review of PubMed and Medline utilizing the keywords: congenital nasolacrimal duct obstruction, nasolacrimal duct obstruction, congenital epiphora, Crigler massage, probing, syringing, silicone tube intubation, inferior turbinate tarsal infracture, balloon dacryoplasty, dacryocystorhinostomy, inferior turbinectomy, nasal endoscopy revealed limited literature on inferior turbinate tarsal infracture. Infracture is a simple, quick, and effective procedure with extremely low morbidity. This study utilizes the large cohort of children for the efficacy and safety of nasal endoscopic guided infracture in cases of CNLDO complicated by the impaction of the inferior turbinate as a first attempt.
SUBJECTS AND METHODS:

ETHICS APPROVAL

This investigation was a retrospective, non-randomized, non-comparative, interventional case series. It was approved by the Institute Review Board. This study adhered to the Declaration of Helsinki.

PATIENT DATABASE, SECURITY AND PROTECTION

Data entry, storage, patient privacy, and statistical analysis were done in accordance with international standards. Data was secured by omitting any personal patient information.

ELIGIBILITY CRITERIA

Consecutive 55 children (69 eyes) with a diagnosis of CNLDO were included. Clinically CNLDO was diagnosed by history, epiphora, increased tear film meniscus height (TMH), recurrent mucoid or mucopurulent discharge either spontaneously or as regurgitation on pressure over lacrimal sac (ROPLAS). To confirm CNLDO, clinically fluorescein dye disappearance test (FDDT) after instillation of proparacaine 0.5% was performed by Katowitz and Welsh technique.7 Children younger than 6 months with CNLDO were advised Crigler massage and chloramphenicol 0.4% antibiotic eye drops four times a day.1 On failure to improve after 6 months of age, they were included in the study. Children with mucocele of the lacrimal sac, dacrocutaneous fistula, history of trauma to lacrimal drainage system, craniofacial anomalies, genetic syndromes, previous history of lacrimal drainage system intervention, lost to follow-up were excluded.

METHODS AND INTERVENTION

For all children, the complete procedure was performed under general anesthesia with
endotracheal intubation. Initially, puncta of both eyes were examined under a microscope, to rule out any punctum stenosis followed by ROPLAS, the characteristics of the refluxed discharge were noted. After which upper punctum was dilated using Nettleship punctum dilator, and probing was done with a Bowman lacrimal probe. After the confirmation of a bony nasolacrimal duct block, the nasal endoscopy was performed to visualize the distal end of nasolacrimal duct, inferior meatus, and the impaction of inferior turbinate. Using a lens spatula the inferior turbinate was medialized towards the nasal septum under visualization. Patency of the nasolacrimal duct was confirmed first by probe visualization on endoscopy and then by syringing (Figure 1).

**FIGURE LEGENDS:**

- Figure 1: Clinical picture showing (A) Punctum dilation using Nettleship punctum dilator, (B) Bony block on nasolacrimal duct probing using Bowman lacrimal probe, (C) Nasal endoscopy, (D) Nasal endoscopic view showing inferior turbinate impaction of inferior nasolacrimal duct with non-visualization of distal end of lacrimal probe, (E) Nasal endoscopic view showing inferior turbinatetarsal infracture using Lens spatula, (F) Nasal endoscopic view showing distal end of probe at nasolacrimal duct meatus, and (G) clinical picture showing post-intervention syringing which was patent.
Patients were placed on antibiotic eyedrops chloramphenicol 0.4 % for four times a day for 2 weeks, tapering steroid eye drops (betamethasone 0.1 %) 6 times a day for 1 week, followed by 4 times a day for 1 week, thrice a day for 1 week, twice a day for 1 week, and then once a day for 1 week, Oxymetazoline (0.05 %) nasal drops for 4 times a day for 1 week and Budesonide (0.2 %) nasal steroid spray for twice a day for 1 week. They were followed up at 1 week, 4 weeks, 3 months, 6 months, and then annually. At each follow-up, visit parents were asked for epiphora, discharge, persistence, or resolution of symptoms. Clinically, children were evaluated for TMH, ROPLAS, and FDDT.

MAIN OUTCOMES AND MEASURES

The outcome was graded as successful with patent syringing on the table and the negative history of epiphora, discharge, and positive FDDT on follow-up at 3 months. It was graded as failed if the child requires any repeat or further intervention on follow up.

STATISTICAL ANALYSIS

Referral data, type of discharge on ROPLAS, diagnosis after the intervention, and successful outcomes were evaluated. The reliability of the measurements within subjects was determined by calculating the standard deviation (SD) using the square-root of the mean within individual variance. Cox regression analysis was used for subgroup analysis of children without the atonic sac to compare the effect of age and duration of symptoms on the successful outcome. All statistical tests were two-sided at a 95 % confidence interval (CI), and a p value < 0.05 was considered statistically significant. SPSS Statistics 20 software released in 2015 was used for all statistical analyses (IBM, Armonk, New York, USA).
RESULTS:

DEMOGRAPHICS

A total of 55 children (69 eyes) presented to us with a mean age of 29.1 ± 15.3 months (median: 27.0; range: 7 - 80 months). They all had symptoms for a mean duration of 27.4 ± 15.8 months (median: 24.0; range: 6 - 80 months). Girls (n = 29, 52.7%) predominated the study. 6 (10.9%) children were referred to us. Rest, 49 (89.1%) came to our centre for a second opinion. Out of which, 31 (63.3%) were advised sac massage, 15 (30.6%) for syringing and probing, and 3 (6.1%) children for DCR. 14 (25.5%) children had bilateral involvement, and among unilateral involvement, the right eye was involved in 17 (30.9%) and left eye in 24 (43.6%).

EVALUATION

All children had increased TMH with 53 eyes (76.8%) having clear fluid reflex on ROPLAS and 16 (23.2%) having mucoid discharge. FDDT was positive in all 69 eyes. On examination under general anesthesia revealed normal puncta with no membranous block of puncta. On probing after punctum dilation revealed bony canalicular block. Following which nasal endoscopy was performed to examine the distal end of nasolacrimal duct, all 69 eyes had inferior turbinate impaction which was medialized by lens spatula. The endpoint of the intervention was the visualization of the lacrimal probe at the inferior meatus. There was mild temporary epistaxis which was spontaneously resolved.

Post-intervention, syringing was performed which was patent in all 63 (91.3%) eyes, but 6 (8.7%) had partial fluid into the nose which was confirmed by the pediatric-size suction catheter placed in the ipsilateral nares along with ballooning of the lacrimal sac and delayed partial regurgitation of clear fluid from the opposite punctum. They were
diagnosed to have an atonic sac and were advised Crigler massage post-operatively.

FOLLOW-UP

The mean follow-up was 44.9 ± 23.8 months (median: 53.0; range: 1 - 77 months). 62 eyes (98.4 %, n = 63 eyes) without atonic sac had complete resolution of CNLDO with 1 (1.6 %) requiring the repeat inferior turbinate tarsal infracture after 2 months, which was subsequently resolved. Out of 6 patients with atonic sac, 2 (33.3 %) were resolved with sac massage, 3 (50 %) needed DCR with earliest requiring it after 4 weeks of intervention, and 1 (16.7 %) developed lacrimal abscess which was managed with incisional and drainage.

SUB-GROUP ANALYSIS OF CHILDREN WITHOUT ATONIC SAC

The mean age was 28.9 ± 13.8 months (median: 30; range: 7 - 58 months) with a mean duration of symptoms of 27.0 ± 14.4 months (median: 24; range: 6 - 58 months). On cox regression analysis, an excellent success rate of 98.4 % of the inferior turbinate tarsal infracture was unaffected by increasing age or duration of symptoms as previously thought (p = 0.918 and p = 0.905, respectively).

DISCUSSION:

Though there is a vast literature on probing efficacy in CNLDO from population-based studies with variable success rate, the availability of studies on inferior turbinate tarsal infracture is limited, specifically in an objective study environment with an accurate diagnosis under direct visualization. Hence, the limitation in using inferior turbinate tarsal infracture effectively as an alternative treatment for CNLDO which may unnecessarily subject a child to DCR. One of the challenges in performing inferior turbinate tarsal infracture using studies in the children has been the difficulty to completely diagnose the inferior turbinate impaction under direct visualization using a nasal endoscope. This
study proposes nasal endoscopic guided inferior turbinate tarsal infracture in children with CNLDO with an excellent success rate.

Mostly, CNLDO occurs due to the maldevelopment or malalignment in the structure of the nasolacrimal duct. There is a variable development in both medial and inferior direction, which may sometimes end up with a fusion of lateral wall of the nasal cavity and inferior turbinate. Hence, the formation of bony obstruction at inferior meatus or inferior nasolacrimal duct.6 Reasoning this, Jones performed inferior turbinectomy in cases of failed probing cases.9

In 1983, Havins and Wilkins reported a 100% success rate with inferior turbinate tarsal fracture as a primary intervention. As a second intervention after a failed probing, they reported 94% success in children with age < 8 months, 76% for 8-18 months, and 56% in children with more than 18 months.8 Katowitz described that the need for inferior turbinate tarsal fracture increases with age, till 6 months there was no need for inferior turbinate tarsal fracture whereas children over 24 months had a mere 1 in 3 success rate with inferior turbinate tarsal fracture.7

Table 1 compares and summarizes the findings of the present study with those of comparable available literature.10–12 Previous studies by Attarzadeh and Khataminia reported the success of inferior turbinate tarsal fracture as insignificant in respect to lacrimal probing which was different from the present study. All previous studies did the intervention without the confirmation of the diagnosis of inferior turbinate impaction by direct visualization. Moreover, in previous literature inferior turbinate tarsal fracture was performed as a blind procedure. That can be one of the reasons for the low success rate of inferior turbinate tarsal fracture in past and hence the acceptance of the completely harmless and quick procedure.
TABLE LEGENDS:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Wesley(10)</th>
<th>Attarzadeh(11)</th>
<th>Khataminia(12)</th>
<th>Mean</th>
<th>Presen t Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size (eyes)</td>
<td>52</td>
<td>42</td>
<td>47</td>
<td>47</td>
<td>69</td>
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<tr>
<td>Number of Children</td>
<td>52</td>
<td>33</td>
<td>47</td>
<td>44</td>
<td>55</td>
</tr>
<tr>
<td>Mean Age (months)</td>
<td>23</td>
<td>20</td>
<td>18</td>
<td>20</td>
<td>29</td>
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<td>Nasal Endoscopy</td>
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<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Resolution of CNLDO</td>
<td>79%</td>
<td>91%</td>
<td>87%</td>
<td>86%</td>
<td>98.4%</td>
</tr>
<tr>
<td>Atonic Sac</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>6</td>
</tr>
<tr>
<td>Months to Acceptable Outcome</td>
<td>N/A</td>
<td>2</td>
<td>3</td>
<td>2.5</td>
<td>3</td>
</tr>
<tr>
<td>Repeat Infracture</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>1</td>
</tr>
<tr>
<td>Dacryorhinostomy</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 1: Comparison with Previous Literature
N/A - Information not Available or Applicable

a – Success rate in children without atonic sac (n=63)
The present study is unique in reporting the diagnosis of congenital atonic sac complicating the CNLDO which was the major reason for the failure of inferior turbinate tarsal fracture and the following need for sac massage and dacryocystorhinostomy in 3 eyes. This needs to be further evaluated in future studies for the natural course of atonic sac in post inferior turbinate tarsal fracture cases.

CONCLUSION:

To summarize our study, we present a large cohort with CNLDO who has undergone inferior turbinate tarsal fracture following initial probing under direct nasal endoscopy. It is a quick, completely harmless intervention with a highly impressive success rate. This may prevent the child from morbid complications of dacryocystorhinostomy. We also report a small group of children with atonic sac that had complicated the CNLDO and was the main reason for the failure of inferior turbinate tarsal fracture. Future studies evaluating the natural course of the atonic sac with a block at various levels in CNLDO and efficacy of their corresponding interventions may help.

REFERENCES:


To Establish The Relationship Between The Structural And Functional Parameters In IIH

Dr. Mousumi Banerjee

AIM:

To determine the correlation between functional parameters and OCT features in patients of idiopathic intracranial hypertension (IIH).

METHODS:

A prospective observational study in early and established cases of papilledema in IIH presenting from December 2017 to February 2019. The inclusion criteria were age >= 18yrs, diagnosed cases of IIH based on modified Dandy criteria. Functional parameters (visual acuity, contrast sensitivity, mean deviation, VER, MfERG) and structural parameters (RNFL,GCL-IPL AND optic disc height) were measured at baseline and at every 6 weeks for 6 months. Patients were advised treatment in the form of weight loss, acetazolamide ranging from 750 / day to 1.5 mg / day as per response, and topiramate as advised by the neurologist.

RESULTS
At baseline, average RNFL values had a moderate negative correlation with mean deviation (r = -0.45, p = 0.0007). RNFL and logMAR visual acuity had a positive co-relation (r = 0.18; p = 0.17), on the contrary baseline GCL and logMAR visual acuity had a negative co-relation (r = -0.4, p = 0.02). Optic disc height (ODH) had a negative correlation with mean deviation (r = -0.46; p = 0.0005).

At six months, ODH values had a positive correlation with visual acuity in logMAR (r = 0.43; p = 0.001). GCL-IPL complex had a positive moderate correlation with contrast sensitivity (r = 0.56; p < 0.001) and mean deviation (r = 0.52; p < 0.001). However, RNFL values did not show any significant correlation with any of the functional parameters.

Baseline GCL-IPL and optic disc height values had a moderate and significant correlation with final functional parameters. However, RNFL did not show any correlation.

Correlation between 6 weeks GCL-IPL and final functional parameters were stronger than that of baseline GCL values.

CONCLUSION:

In the setting of severe papilledema, RNFL can misguide the prognosis. Despite the limitation, the GCL-IPL thickness can be a valuable tool for an objective evaluation of the integrity of the optic nerve in patients with IIH and ODH may be used as an alternative or in combination with GCL-IPL in these cases.

INTRODUCTION

Optical coherence tomography (OCT) is a non-invasive, noncontact trans-pupillary imaging technology providing high resolution, cross-sectional images of ocular and biological structures to visualize and measure anatomic layers of the retina. It is a useful investigation to diagnose and monitor the cases of papilledema.¹²
Serial monitoring of peripapillary Retinal Nerve Fibre Layer (RNFL) thickness may provide a quantitative, objective, and sensitive measurement of changes in the papilledema \(^3\) especially when the patient is seen by different care providers. A reduction in peripapillary RNFL thickness can be a result of the improvement of papilledema or worsening axonal loss from disease progression. Combining the macular ganglion cell layer-inner plexiform layer thickness (GCL-IPL) with the peripapillary RNFL thickness allows one to evaluate for optic neuropathy in the presence of papilledema. \(^4\) Successful treatment with the protection of neuroaxonal structure will cause a reduction in the peripapillary RNFL thickness with a preserved macular GCIP thickness. However, a concordant reduction in the RNFL thickness and macular GCIP thickness indicates worsening optic neuropathy and could be an indication of treatment failure. \(^5\)

**MATERIALS AND METHODS**

The study was a prospective observational study done in a tertiary eye care center undertaken in early and established cases of papilledema in IIH recruited from the outpatient department and neuro-Ophthalmology clinic and neurology OPD of a tertiary care center presenting from December 2017 to February 2019.

Institutional ethics committee approval was obtained from the Institutional Review Board/ Ethics Committee. The research was conducted adhering to the tenets of the Declaration of Helsinki and informed consent was taken from the patients and healthy controls. The inclusion criteria were age \(\geq 18\) yrs, diagnosed cases of IIH based on modified Dandy criteria, \(^6\) early and established cases.

Patients with evidence of hydrocephalus, space-occupying lesion, structural/vascular lesion, venous sinus thrombosis on MRV, pre-existing optic neuropathies including glaucoma and glaucoma suspects, dense media opacification (e.g. cataract) precluding precise ocular and OCT examinations, patients with chronic and atrophic papilledema
and patients not willing giving consent were excluded from the study.

Details regarding the onset, progression and duration of symptoms, and presence of pre-existing co-morbidities were recorded. Patients were advised treatment in the form of weight loss, acetazolamide ranging from 750/day to 1.5 mg/day as per response, and topiramate as advised by the neurologist.

Best-corrected visual acuity was recorded with the ETDRS chart (Early Treatment Diabetic Retinopathy Study). Slit-lamp anterior segment examination and posterior segment examination was performed by 90D slit lamp bio-microscopy. Magnetic resonance Imaging with contrast was performed to rule out any space-occupying lesion. Optic nerve function tests were performed which included color vision (Ishihara pseudo isochromatic plates 1997 version; Kanehara & Co., Ltd., Tokyo, Japan), contrast sensitivity (Pelli-Robson chart), and visual field charting (30-2 SITA Standard, Humphrey, San Leandro, CA). Pattern-reversal Visual Evoked Response (VER) and multifocal electroretinogram (Metrovision Monpack, Pierenchies, France) were also performed.

Spectral-domain OCT (Cirrus HD-OCT Model 4000; Carl Zeiss Meditec Inc., Dublin, CA) was performed in all cases and controls. Retinal nerve fiber layer thickness was measured with the RNFL scan centered on the optic disc (optic disc-cube 200 x 200 volume scans), average RNFL values were used for final correlation. Macular Ganglion Cell Layer- Inner Plexiform Layer thickness was evaluated with the help of the automated algorithm of Cirrus HD-OCT Model 4000 (Carl Zeiss Meditec Inc., Dublin, CA) centered on the fovea (512 x 128 volume scans). For optic disc height (ODH) 5 line raster scan with 5 horizontally oriented line of length 9 mm, separated by 0.5 mm spread across the entire surface of the optic disc was used and was measured by manually placing a vertical line from a line connecting the RPE layer, temporal and nasal neural canal borders to the top of ONH. The average value of the 5 lines was considered to be the mean optic disc height.
All scans had a signal strength of a minimum of 6 and scans were repeated if any motion artefact was noted. (Figure 1)

The ocular parameters were measured at baseline and every 6 weeks for 6 months.

ANALYSIS

The data was collected in a predesigned proforma and spread on Microsoft Excel Worksheet and statistical analysis of the study was done using SPSS IBM Statistical Package software version 21.0. Descriptive statistics; mean, median, range were used to summarize the various variables at baseline and 6 months. Mann Whitney test and student t-test were used for comparing non-parameteric and parametric data. Multiple linear regression was done to analyze the changes in various parameters for 6 months. Correlation between two variables was analyzed with Spearman correlation and Pearson correlation for non-parametric and parametric data respectively. The p-values of <= 0.05 were considered to be significant.

RESULTS

The mean age of patients in our study was 31 ± 7.53 years, our study included 21 females and 6 males. The mean duration of symptoms in our cases was 4.5 months. Headache constituted the most common symptom which was present in 90.7 % of our cases followed by transient visual obscurcation (TVO) in 40.7 %. Other symptoms were diminution of vision in 29 % and diplopia in 20.3 %.

There was a significant difference in OCT and functional parameters between cases and control at baseline (table 1). A reduction in RNFL thickness and disc height was noted over 6 months.
<table>
<thead>
<tr>
<th>STRUCTURAL PARAMETERS</th>
<th>CASES at baseline (N=54 EYES)</th>
<th>CONTROL S at baseline (N=80 EYES)</th>
<th>P VALUE</th>
<th>CASES at 6 months</th>
<th>CONTROL S at 6 months</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNFL (µm)</td>
<td>269.97 ± 91.09</td>
<td>88.11 ± 2.17</td>
<td>&lt;0.001</td>
<td>93.35 ± 27.58</td>
<td>88.11 ± 2.17</td>
<td>0.16</td>
</tr>
<tr>
<td>RGCL-IPL complex (µm)</td>
<td>63.35 ± 23.58</td>
<td>79.85 ± 3.31</td>
<td>&lt;0.001</td>
<td>73.96 ± 11.1</td>
<td>79.85 ± 3.3</td>
<td>0.0003</td>
</tr>
<tr>
<td>Optic disc height(µm)</td>
<td>1053.18 ± 207.03</td>
<td>0 ± 0</td>
<td>&lt;0.001</td>
<td>444.44 ± 218.66 (median: 448)</td>
<td>0 ± 0</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FUNCTIONAL PARAMETERS</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BCVA (logMAR)</td>
<td>0.13 ± 0.16</td>
<td>0 ± 0</td>
<td>&lt;0.001</td>
<td>0.02 ± 0.06 (median: 0)</td>
<td>0 ± 0</td>
<td>0.01</td>
</tr>
<tr>
<td>Contrast sensitivity</td>
<td>1.466 ± 0.028</td>
<td>1.66 ± 0.005</td>
<td>&lt;0.001</td>
<td>1.59 ± 0.10</td>
<td>1.66 ± 0.003</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Colour Vision</td>
<td>Normal - 75.93%</td>
<td>Normal - 100%</td>
<td>-</td>
<td>Normal - 92%</td>
<td>Normal - 100%</td>
<td>-</td>
</tr>
<tr>
<td>--------------</td>
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</tr>
<tr>
<td>Mean deviation</td>
<td>-9.92±6.82</td>
<td>-1.90 ± 0.441</td>
<td>&lt;0.01</td>
<td>-4.60±5.5 (median : -2.95)</td>
<td>-1.90±0.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pattern standard deviation</td>
<td>6.21±0.45</td>
<td>1.85±0.45</td>
<td>&lt;0.01</td>
<td>3.51±0.51</td>
<td>1.85±0.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VER amp P100(µV)</td>
<td>7.13±3.14</td>
<td>14.70±1.03</td>
<td>&lt;0.01</td>
<td>11.33±3.75</td>
<td>14.70±1.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VER latency P100(ms)</td>
<td>121.10±1.02</td>
<td>100.53±2.12</td>
<td>&lt;0.01</td>
<td>107.59±8.95</td>
<td>100.53±2.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>mfERG P1amp(NV)</td>
<td>895.16±5.3</td>
<td>1669.85±284.19</td>
<td>&lt;0.01</td>
<td>1303.88±565.72</td>
<td>1669.85±284.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MfERG P1</td>
<td>48.03±3.959</td>
<td>42.66±0.917</td>
<td>&lt;0.01</td>
<td>44.7±1.847</td>
<td>42.46±0.917</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 1: Structural and functional parameters between cases and controls at baseline and at 6 months
CORRELATION AT BASELINE

At baseline, average RNFL values had a moderate negative correlation with mean deviation ($r = -0.45$, $p = 0.0007$) and a moderate positive correlation with VER P100 latency ($r = 0.35$, $p = 0.008$). At baseline RNFL and logMAR visual acuity had a positive co-relation ($r = 0.18$, $p = 0.17$), on the contrary baseline GCL and logMAR visual acuity had a negative co-relation ($r = -0.4$, $p = 0.02$). Baseline GCL-IPL thickness values had moderate positive correlation with contrast sensitivity ($r = 0.34$, $p = 0.01$) and mean deviation ($r = 0.4$, $p = 0.002$) and a negative moderate correlation with mfERG implicit time (IT) of P1 wave ($r = -0.41$, $p = 0.0019$). Optic disc height at baseline had a negative correlation with mean deviation ($r = -0.046$, $p = 0.0005$) and a positive moderate correlation with VER P100 latency ($r = 0.55$, $p < 0.001$). (Table 2)

CORRELATION AT 6 MONTHS

At six months, optic disc height values had a positive correlation with visual acuity in logMAR ($r = 0.43$, $p = 0.001$). GCL-IPL complex at six months had a positive moderate correlation with contrast sensitivity ($r = 0.56$, $p < 0.001$) and mean deviation ($r = 0.52$, $p < 0.001$). However, RNFL values did not show any significant correlation with any of the functional parameters at six months. (Table 2)
### Table 2: Correlation between structural and functional parameters at baseline and at 6 Montha

<table>
<thead>
<tr>
<th>Structural parameters</th>
<th>Visual acuity</th>
<th>Contrast sensitivity</th>
<th>Mean deviation</th>
<th>VER P100 amp</th>
<th>VER P100 latency</th>
<th>mfERG P1 amp</th>
<th>mfERG P1 implicit time</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNFL</td>
<td>r=0.03; p=0.78</td>
<td>r=0.2; p=0.1</td>
<td>r=0.17; p=0.2</td>
<td>r=-0.17; p=0.2</td>
<td>r=-0.33; p=0.01</td>
<td>r=-0.35; p=0.007</td>
<td>r=-0.2; p=0.14</td>
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<tr>
<td>GCL-IPL</td>
<td>r=-0.28; p=0.03</td>
<td>r=0.54; p&lt;0.0001</td>
<td>r=0.52; p&lt;0.0001</td>
<td>r=-0.17; p=0.2</td>
<td>r=-0.27; p=0.04</td>
<td>r=0.02; p=0.08</td>
<td>r=0.01; p=0.9</td>
</tr>
<tr>
<td>OD height</td>
<td>r=0.4; p=0.001</td>
<td>r=-0.01; p=0.9</td>
<td>r=-0.12; p=0.34</td>
<td>r=-0.19; p=0.18</td>
<td>r=-0.13; p=0.32</td>
<td>r=0.1; p=0.4</td>
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</tr>
</tbody>
</table>
Baseline structural parameters vs final outcome correlation

Baseline GCL-IPL and optic disc height values had a moderate and significant correlation with final mean deviation ($r = 0.354; p = 0.006$ and $r = -0.44; p = 0.0007$ respectively), contrast sensitivity ($r = 0.33; p = 0.01$ and $r = -0.35; p = 0.01$ respectively), visual acuity ($r = -0.37; p = 0.005$ and $r = 0.41; p = 0.002$ respectively) whereas RNFL did not show any correlation with final functional parameters in our study. The correlation between structural and functional parameters at different time points have been summarized in Figure 3. In addition to correlation with baseline GCL-IPL we correlated the visual function with GCL-IPL at 6 weeks. The correlation coefficient and $p$ value for visual acuity, mean deviation and contrast sensitivity was $r = -0.34, p = 0.01; r = 0.44, p < 0.001$ and $r = 0.45, p < 0.001$ respectively.

Discussion

The emerging popularity of the use of OCT in neuro-ophthalmic disorders is due to its ability for excellent imaging of each layer of the retina and optic disc. The present study was conducted to observe the changes in OCT parameters and their relationship with the functional parameters.

RNFL thickness is a commonly used parameter for the detection and monitoring of papilledema. RNFL thickness is increased in patients with IIH due to the axoplasmic flow stasis \(^8\) and in both short and long term follow up, RNFL thickness has been noted to normalize \(^9\). In the present study, the RNFL thickness was significantly higher than control at the baseline and progressively decreased over 6 months suggestive of resolution of papilledema.

Unfortunately, the OCT-derived RNFL thickness alone sometimes does not differentiate treatment response from the development of optic atrophy. \(^10\) Ganglion cell layer–inner
plexiform layer (GCL-IPL) specifically helps to evaluate the integrity of the optic nerve in the setting of disc edema.\(^5\) Thinning of the GCL-IPL complex in presence of normal RNFL may be suggestive of optic atrophy.\(^1\) In our study, we found that mean GCL-IPL thickness was significantly low as compared to controls at baseline as well as at 6 months follow-up, while the RNFL thickness at 6 months was not significantly different from the control group. 59.25 % of patients had GCL within 2SD of the control group, 40.74% had lower value at 6 month follow up. A similar observation has been made by Bianchi et al and Dalia et al where they have reported that 10% and 13% of their patients respectively in various stages of papilledema had thinner GCL-IPL even when the RNFL was still elevated.\(^{11,12}\) Athappilly G also reported a similar observation in their 18 patients where they found GCL-IPL was significantly thinner than the control group at all time points, while RNFL was significantly thicker at initial stages.\(^{13}\) Interestingly, on the linear analysis, we found that GCL-IPL thickness showed statistically significant improvement from baseline value to that of six weeks follow up, followed by an improving trend over the six months though the difference was not significant after six weeks.

Both RNFL and GCL-IPL layers showed a significant correlation with mean deviation at baseline. GCL-IPL also showed a moderate correlation with visual acuity and contrast sensitivity at baseline. At 6 months RNFL did not show a significant correlation with any of the visual functional parameters. At six months GCL-IPL layer showed moderate correlation with mean deviation and contrast sensitivity, thus the role of GCL IPL thickness as a structural parameter for indirect assessment of functional parameters cannot be ruled out.

Rebolleda et al in their study found a significant correlation between baseline RNFL and final mean deviation at one year. They reported that the mean RNFL at 1 year had normalized in 90% of eyes with a statistically significant inverse correlation with baseline mean
deviation. Skau et al also reported a similar correlation between change in RNFL over 3 months with change in mean deviation. Both of these studies were done on the stratus model of OCT in which GCL-IPL evaluation was not available. To understand the predictive value of baseline OCT parameters, a correlation between the baseline structural parameters with the final visual functions were sought. Baseline GCL-IPL values showed a significant correlation with the final visual acuity, mean deviation, and contrast sensitivity. However, baseline RNFL thickness did not show a statistically significant correlation with any of the final visual functional parameters. Since there was a significant improvement in the GCL-IPL layer between baseline and 6 weeks follow up, we correlated the final functional parameters with GCL-IPL at 6 weeks and interestingly the relationship was stronger at this time point (visual acuity $r = -0.34$, $p = 0.01$; Mean deviation $r = 0.44$, $p < 0.001$ and contrast sensitivity $r = 0.45$, $p < 0.001$). Athappilly G et al in their retrospective study also found that baseline RNFL did not correlate with the final mean deviation ($r = 0.012$; $p = 0.95$). Nonetheless, they also observed that the GCL-IPL layer thickness at the second visit significantly correlated with final mean deviation albeit at one year ($r = 0.47$; $p = 0.007$). Chen et al in their retrospective study of 31 patients with visual acuity of less than 25/20, also observed a similar relationship between the mean deviation and GCL-IPL measured by Iowa protocol. Interestingly they also found that GCL-IPL at 2-3 weeks correlated better with the final visual outcome.

Even though all these studies including the present study have heterogeneity in their methodology, the results indicate that GCL-IPL may be used as a marker to predict the final visual outcome in patients of IIH. Contrary to these results, IIHTT has reported no significant correlation between OCT parameters and visual function. The study included patients with only mild visual field defects (PMD of “2.00 dB to “7.00 dB) which might explain the dissimilar results.

The Iowa 3D segmentation protocol to measure RNFL and GCL-IPL requires superior
technical skills and is time-consuming to be replicated in a busy outpatient department. However, optic disc height (ODH) evaluated by IIHTT using 5 line raster scan seemed to be a faster and simpler method of assessment of optic disc edema. The optic disc height was measured manually for each line and an average of 5 lines was considered for final evaluation. The study reported a strong correlation of ODH with peripapillary RNFL thickness and total retinal thickness. In our study, we followed the same method and found a strong and significant correlation of ODH with RNFL and GCL-IPL layer [0.622 (< 0.001) and -0.604 (< 0.001)]. ODH gradually decreased over 6 months and showed a good correlation with visual functional parameters. At baseline it had a significant negative correlation with mean deviation (r = -.046; p = 0.0005) and a positive moderate correlation with VER P100 latency (r = 0.55; p < 0.001). At six months, it had a positive correlation with visual acuity in logMAR (r = 0.43; p = 0.001). The baseline ODH showed moderate and significant correlation with mean deviation (r = -.44; p = 0.0007), contrast sensitivity (r = -0.35; p = 0.01), visual acuity (r = 0.41; p = 0.002) which was equal (or marginally more) to that of GCL-IPL layer in strength. These results suggest that till a more robust segmentation algorithm for measurement of RNFL and GCL layer becomes available, ODH may be used as a tool to monitor and prognosticate patients of IIH.

Limitations of our study include relatively small sample size and use of the commercial algorithm for measurement of RNFL and GCL layer.

CONCLUSION

It is a matter of time before the commercially available algorithms become more reliable because of the increased resolution of OCT and improved segmentation algorithms. For the time being, it is important to be able to identify artifacts in the GCL-IPL measurements, particularly in presence of disc edema. In the setting of severe papilledema, RNFL can misguide the prognosis. Despite the limitation, the GCL-IPL thickness can be a valuable
tool for an objective evaluation of the integrity of the optic nerve in patients with IIH and ODH may be used as an alternative or in combination with GCL-IPL in these cases.

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Artificial Intelligence And Wolfram Language In Papilloedema

Dr. Harshavardhan Ghorpade

INTRODUCTION:

Detection of papilloedema and the ability to determine that the optic disk is normal is valuable in the evaluation of patients with headache and other neurologic symptoms. Diagnosis of papilloedema on ophthalmoscopy determines the diagnostic strategy and treatment options. Mistakes made in detecting papilloedema usually can cause visual loss. Artificial intelligence is a useful adjunct in clinical practice. The use of artificial intelligence to detect papilloedema from fundus photographs has not been well studied.

PURPOSE:

To study Conventional Artificial Intelligence tools Vs Wolfram language analysis of papilloedema for prognosis prediction in surgical and non surgical management.

METHODS:

At four tertiary centers in Mumbai and Navi Mumbai we trained, validated and tested a Wolfram language deep-learning system to classify optic disks as being normal or having
papilloedema or other abnormalities from 16,783 fundus pictures taken after pupillary dilatation. 15,873 from 21 sites in 11 hospitals were used for training and validation. Performance at classifying the optic-disk appearance was evaluated by calculating the area under the receiver-operating-characteristic curve (AUC), sensitivity and specificity as compared with a reference standard of clinical diagnoses by two separate ophthalmologists.

291 eyes with due to various reasons were analysed by standard artificial intelligence and Wolfram language analysis. Multiple regression analysis was performed on these cases to analyse factors which are important in prognosis and correlated with clinical tools. The predictions made by the algorithms were compared with actual results in actual cases.

RESULTS:

In the validation set, both systems discriminated papilloedema from normal disks with an AUC of 0.98 (95% confidence interval [CI], 0.97 to 0.99) and normal from abnormal disks with an AUC of 0.97 (95% CI, 0.96 to 0.99). The predictive algorithm has a sensitivity of 89% and specificity of 82% with conventional Artificial intelligence and the Wolfram language analysis has sensitivity of 84% and specificity of 89%. And when combined, the algorithms were able to predict the results with 90% accuracy. The factors which were found to contribute most were age, weight, myopia/hypermetropia, type of ailment, duration of ailment, visual acuity, duration of treatment.

DISCUSSION:

Many studies have discovered that direct ophthalmoscopy can be replaced by ocular fundus digital cameras that provide high-quality photographs of the optic nerve and retina, even without pharmacologic dilatation of the pupil. Most deep-learning research
in ophthalmology has been for screening of retinal disorders and glaucoma. Some authors have shown that deep-learning systems could recognize right from left optic disks in the presence of optic-nerve abnormalities on fundus photographs, could discriminate disks with papilloedema from normal disks with an average accuracy of 93% (similar to the value in our study 37) and could differentiate true optic-disk swelling from pseudo-swelling with an accuracy of approximately 95%.

Wolfram language is a simple language recently developed for easier interpretation.

None have used Wolfram language as yet for papilloedema and ours is the first study to do so.

CONCLUSION:

Combination of conventional Artificial Intelligence and deep machine learning by Wolfram language can be used to predict whether surgery is needed and can be correlated with clinical tools.

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Orbital Mass As Presenting Sign Of Underlying Malignancy: Clinical, Pathological Features & Outcomes

Dr. Akshay Gopinathan Nair, Dr. Nita A Shah, Dr. Indumati Gopinathan, Dr. Anil Tibrewal, Dr. Rima S Pathak, Dr. Sundaram Natarajan, Dr. Vandana Jain

INTRODUCTION:

Orbital metastatic tumours are relatively uncommon, and the clinical presentation and radiological features depend on the primary site. Tumours that metastasise to the orbit are estimated to account for up to 13% of all orbital tumours. [1-4] It has been reported that over the natural course of the disease, between 2-5% of all cancer patients may develop an orbital metastatic lesion. [5] The most common route for spread of the tumour from its primary origin to the orbit is the haematogenous route. The most common primary site is breast, followed by the lung and prostate. [4] Other uncommon sites include the kidneys, pancreas, cervix, thyroid, stomach and melanomas. [6-10] While most patients who present with orbital metastatic lesions have a pre-existing diagnosis of a primary tumour between 15 - 42% of patients, the orbital mass is the presenting sign of a previously undiagnosed tumour. [4,11,12] Common presenting features of orbital metastatic tumours include diplopia, pain, proptosis, reduced vision, ptosis and a palpable mass lesion. [1,5] The prognosis of
orbital metastases has remained largely unchanged over the past few decades: Valenzuela et al. reported that survival was limited to 1.5 years after initial diagnosis, independent of the histological type; with 29% of patients in their cohort were alive after 17 months.\textsuperscript{12} In this communication we present the clinical and the pathological features along with outcomes of patients in whom an orbital mass was the presenting feature of an underlying malignancy.

METHODS:

This retrospective study was approved by the local institutional review board which waived informed consent. The report adhered to the ethical principles outlined in the Declaration of Helsinki as amended in 2013. The study cohort composed of all patients diagnosed with orbital metastatic tumours between 2014 and 2019. Data on lesion type and location, surgery performed, presenting complaints, histopathological diagnoses, comprehensive ophthalmic examination findings, clinical photographs, systemic history and Positron Emission Tomography - Computed Tomography (PET/CT) findings were collected and analyzed.

RESULTS:

I. DEMOGRAPHICS:

In all 30 cases, orbital metastatic tumours were diagnosed. Of these, 20 (66.7%) cases had a previous diagnosis of a malignancy. 10/30 (33.3%) had no prior history of cancer. These ten patients in whom the orbital metastasis was the presenting feature of previously undiagnosed systemic malignancy was the primary analysis group. The mean follow-up was 7.8 months. All patients diagnosed as orbital metastatic tumour underwent a PET-CT scan, oncology consult and subsequent management as per the multidisciplinary tumour board’s recommendation. In these 10 cases, lung (4/10; 40%) was the most common
primary site followed by breast (3/10; 30%). One case each of primary prostatic cancer, adenocarcinoma of the gallbladder and primary melanoma of the colon were noted. In this cohort, (6/10) 60 % of the patients for female the mean age presentation was 68 years with a range of 52 - 77 years.

Clinical features:

The most common presenting complaint was proptosis (90 %) followed by diplopia (60 %), ocular pain (50 %), vision loss (40 %) and mass lesion (30 %). The mean duration from initial orbital symptom to the final diagnosis of an orbital metastatic tumour was 2.25 months (range: 1 - 6 months). As mentioned earlier, all patients underwent a systematic evaluation that included PET/ CT scans. The mean number of metastatic sites involved at the time of diagnosis of the orbital lesion was 3.3. A detailed systemic history was elicited from all patients – it was observed that 7/10 (70 %) of the patients had no systemic complaints related or attributable to their primary tumour. Lower back pain, constipation and severe headache were observed in one patient each and these symptoms were retrospectively attributable to their primary or metastatic tumours.

MANAGEMENT AND OUTCOMES:

In terms of management, 8 out of 10 patients underwent an incision biopsy of the orbital mass. One patient underwent a PET/ CT scan prior to orbital biopsy which was suspicious of a primary mass lesion in the abdomen. This was followed by an exploratory laparotomy which led to the diagnosis of a primary adenocarcinoma of the gall bladder and an FNAC of the orbital mass subsequently confirmed the diagnosis of orbital metastasis. One patient presented with vision reduction and was found to have a breast mass the patient underwent a PET/ CT scan which showed orbital, brain and spinal metastatic lesions. All patients underwent multimodal management, based on the advice of a medical and radiation oncologists. All 10/10 patients received chemotherapy for the primary cancer.
additionally four patients underwent radiotherapy. Three (30%) patients also underwent surgery of the primary lesion, which was either to confirm the diagnosis of the primary tumour or palliative in nature.

Telephonic follow-up was carried out and it was noted that 8/10 (80%) of the patients had died due to disease and in this subset of patients whose death was attributable to the primary cancer, the mean duration from diagnosis of tumour to death was 5.8 months.

DISCUSSION:

To the best of our knowledge this is the first series from India documenting the clinical features and outcomes of patients whom the orbital lesion was the presenting feature of a disseminated underlying malignancy. The clinical manifestations of orbital metastasis or fairly common and similar across all series. The patients typically present with sudden onset diplopia, reduced vision, visible or palpable lump beneath the eyelid or the orbital margin along with pain. [4,5,13] Clinical examination in these patients typically reveals proptosis and displacement of the globe with a palpable mass. The key features in these cases are the rapid onset and severity of symptoms which indicate a progressive and aggressive disease process. Additionally, pain and other inflammatory signs which would be suggestive of orbital inflammatory disease are absent.

El-Hadad and colleagues reported the multidisciplinary management of orbital metastasis and survival outcomes of 118 patients. [14] In their series, 22/118 (19%) patients presented with orbital metastasis as the first manifestation of metastatic cancer. They have mentioned that this is at the lower end of the spectrum of figures reported in literature mainly due to the fact that their study was from a comprehensive cancer care hospital where patients are more likely to have a diagnosis of cancer than in series generated from eye hospitals. Indeed, other studies have shown that in up to a third of all orbital metastatic tumours, the primary tumour remains unknown despite systemic evaluation and long follow-up.
However, in our series the final histopathological diagnosis was obtained in all cases.

In our series we found that the average number of metastatic sites that were identified on imaging was 3.3. This indicates that the underlying malignancy was fairly advanced and disseminated prior to diagnosis. In the series by El-Hadad and colleagues, they reported that 40% of all their patients with orbital metastasis had oligo metastatic disease. This meant that the orbit what is the only identifiable site of metastasis (in a patient with a previously treated cancer).[14]

Char and colleagues have reported that in their series, the median survival was 1.3 years amongst all patients of orbital metastasis and the two-year survival rate was 27%. [17] They also noted that there was no significant difference in survival duration between patients with and without a known primary tumour at the time the orbital metastasis was diagnosed. In contrast, our data showed that patients with orbital metastases and a previous diagnosed cancer at the time of presentation, the mean survival was 12.3 months. In contrast, the mean survival was only 5.8 months among those with no known primary. This difference was statistically significant (p < 0.005); age and gender were not found to play any significant role in the overall survival. In both groups in our study, lung and breast were the most common primary sites.

It was noted in our series that 7 out of 10 patients did not report any systemic signs or symptoms that could be attributable to the primary tumour. It is likely that the patients were unaware or disregarded early warning symptoms. Surveys conducted to assess the level of awareness and knowledge about cancers and associated risk factors among households in India have shown that among many communities there is a very low level of awareness about warning signs and symptoms. [18] Poor awareness often leads to poor uptake of screening modalities and delay in seeking help for cancer like symptoms. [19]
In summary, we present our findings in patients who presented with an orbital mass as the first sign of an underlying disseminated malignancy which was previously undiagnosed. These patients were found to have aggressive disease; poorer prognosis with significantly shorter survival as compared to patients with orbital metastasis with a previous cancer diagnosis. Patients with complaints of recent onset proptosis, diplopia and orbital pain along with a palpable mass lesion should be treated with a high degree of suspicion for orbital metastatic tumours.

**LEGEND:**

Figure 1: A graphical representation of the clinical features of the patients.

Figure 2: External photograph of a 67-year-old male who presented with left sided sudden onset proptosis, diplopia, reduced vision and chemosis (Figure 2A). MRI showed a heterogeneous mass in the superomedial orbit displacing the globe downwards and outwards (Figures 2B, 2C). Contrast enhancement is seen and in the centre of the mass, a hyper intense focus is seen. An incisional biopsy confirmed the diagnosis of metastatic adenocarcinoma of the lung. The patient had secondaries in the liver and the orbit in addition to regional lymph node involvement.
REFERENCES:


Anti Dysphotopsia Lens (ADL) - A Novel Intraocular Lens Design To Prevent Dysphotopsia Post Cataract Surgery.

Dr. Prabhakar GV, Dr. J K Reddy

ABSTRACT:

1) PURPOSE:

To design and evaluate a new intraocular lens to prevent negative dysphotopsia in the form of a temporal crescentic shadow post cataract surgery.

2) METHODS:

Most accepted theory of dysphotopsia is the presence of a gap between iris and optic which leads to a grey shaded area formed between the ray missing IOL and the ray refracted by IOL, causing a temporal crescentic shadow. Our concept was to give a normal crystalline lens profile to IOL optic by eliminating the gap between IOL and iris which simulates reverse optic capture or better. The new IOL is of hyperbola shape where optic comes in contact with pupil margin after implantation in the capsular bag thereby eliminating the space that light rays can pass through and produce negative
dysphotopsia. The lens was implanted in 56 patients in whom the other operated eye had negative dysphotopsia.

3) RESULTS:

None of the 56 patients (at 1 year) complained of any dysphotopsia in which ADL lens was implanted.

4) CONCLUSION:

This study suggests that new IOL design is effective in eliminating negative dysphotopsia.

INTRODUCTION:

Unwanted optical phenomena such as negative and positive dysphotopsias are well known side effects after cataract surgery \(^{(1)}\). Negative dysphotopsia is defined as the perception of a shadow obscuring the temporal field of vision, while positive dysphotopsia is characterised by halos, arcs or streaks around point light sources \(^{(2,3)}\).

In the majority of cases, dysphotopsias resolve or diminish over time. Therefore, waiting and reassurance are reasonable initial treatment strategies. However, in 0.2 to 1 \% of pseudophakic patients, severe symptoms will persist \(^{(2,4)}\) and additional surgery may be required.

Our idea was to design a new intraocular lens eliminating the factors causing dysphotopsia. Most accepted theory of dysphotopsia is the presence of a gap between iris and optic which leads to a grey shaded area formed between the ray missing IOL and the ray refracted by IOL, causing a temporal crescentic shadow.
Our concept was to give a normal crystalline lens profile to the IOL optic, to eliminate gap between IOL and iris which simulates reverse optic capture or better. The new design IOL is hyperbola shape, like a contact lens, with no junction between the optic and haptic with convexity facing anteriorly (fig 1-4) The optic comes in contact with pupil margin after implantation in the capsular bag there by eliminating the space that light rays can pass through and produce negative dysphotopsia.

METHODS:

All patients underwent uneventful phacoemulsification with our IOL implantation in the capsular bag. Complaints of dysphotopsia were noted before surgery and at each follow-up visit. Evaluation included uncorrected (UDVA) and corrected (CDVA) distance visual acuity, manifest refraction, Goldman applanation tonometry, slit-lamp examination, Scheimpflug photography (Pentacam, Oculus Optikgeräte GmbH, Wetzlar, Germany) and Anterior segment optical coherence tomography (Cirrus, Carl Zeiss Meditec, Inc, Dublin, CA).

Informed consent was obtained from all the participants. Study protocols adhered to the declaration of Helsinki and was conducted after getting approval from the ethical committee.

Fig 1: Showing ADL lens with central optic and 360 degrees continuous haptic angulated posteriorly and two dialling holes.
Fig 2: showing ADL lens postoperatively highlighting the proximity between optic and rhexis margin

Fig 3: showing normal crystalline lens profile of capsular bag after ADL lens implantation.
DISCUSSION

The current treatment options for severe persistent negative dysphotopsia include IOL exchange with placement of a secondary IOL in the bag or in the ciliary sulcus, implantation of a supplementary IOL, reverse optic capture and Nd: YAG anterior capsulectomy. However, in some cases the symptoms may persist after treatment (2, 4-12). We have shown that implantation of our ADL lens can successfully treat negative dysphotopsia. Negative dysphotopsia occurs with IOLs of different materials (2,5,10,11) with both rounded and squared edges (2,10,13). Some patients might develop a unique interaction between the optical pathways of the eye and the IOL (4). One possible mechanism is the reflection of light rays between the IOL edges and the anterior capsulorhexis, which can be successfully treated with reverse optic capture.

A large distance between the anterior surface of the IOL and the posterior iris surface also play a role (3,14). The reduction of this distance is achieved by implantation of ADL lens and hence negative dysphotopsia was avoided in all cases.

RESULTS:

ADL lens was implanted in 56 patients with negative dysphotopsia in the other eye (fig 5). The mean age of the patients was 63.0 ± 6.6 years. None of the patients experienced negative dysphotopsia post-surgery.

Fig 4: OCT image showing that there is no gap between optic and iris, thus eliminating the gap for rays to pass through
Fig 5: graph highlighting the results showing that none of the patients experienced negative dysphotopsia post ADL lens implantation.

None of the patients had pupillary block, IOP rise or pigmentary dispersion.

CONCLUSION:

Implantation of the ADL lens is a safe and effective treatment of negative dysphotopsia. ADL lens eliminates the gap between optic and pupil. Thus, there is no space for rays to pass through thereby eliminating the chances of dysphotopsia.

REFERENCES


Clinical, Pathologic Features and Management of Advanced Eye and Orbital Plasmacytoma

Dr. Harika Regani

KEYWORDS:

Orbital Plasmacytoma, Multiple Myeloma, CD138, Plasma cells

ABSTRACT:

PURPOSE:

Multiple myeloma (MM) is the second most common haematological malignancy, usually affecting patients more than 40 years of age. Extramedullary plasmacytoma is a rare manifestation of multiple myeloma and may be associated with poor visual and clinical outcomes. This article describes the clinical, pathological, radiological diagnosis and management in these patients.
METHODS:

This is a retrospective observational and interventional case series of six patients of Orbital Plasmacytoma from 2013 to 2019 at a tertiary eye care centre in India. Medical records were reviewed for patient information including demographics, clinical features, radiological features, pathological features and the course of management.

RESULTS:

Male to female ratio was 2:1. Mean age at the time of diagnosis was 55.5 years (Range: 20-74 years). The presentation was unilateral in five (83.3 %) and bilateral in one (16.7 %) patient. Three patients (60 %) presented with acute onset of diplopia and proptosis. Radiologically all the lesions (100 %) were in anterior orbit involving both inferior and superior quadrant equally (50 %). Three patients (50 %) had an association with Multiple Myeloma and three (50 %) were solitary plasmacytoma. Incisional biopsy was done in all the patients (100 %) to confirm the diagnosis. External beam radiotherapy (EBRT) was given in four patients (Pre incisional biopsy EBRT was done in 2 (33.3 %) and post incisional biopsy EBRT was done in 2 (33.3 %) patients. Chemotherapy with Bone marrow transplantation was done in one patient. At a mean follow up of 13.6 months, all the patients (100 %) had good visual acuity.

CONCLUSION:

Early diagnosis with a multidisciplinary approach fairly increases the chances of vision salvage and provides a decent quality of life to the patient.

INTRODUCTION

Plasmacytomas constitute 5 - 10 % of all plasma cell neoplasms and only 1% of orbital tumors. Orbital Plasmacytoma is an uncommon presentation of multiple myeloma and
in more than half of the cases, it is only discovered after diagnosis of multiple myeloma. Multiple myeloma is a tumor of malignant plasma cells that is considered as the second most common hematologic malignancy.\textsuperscript{[1]} Plasmacytomas without multiple myeloma have been classified by the International Myeloma Working group in 2003 into three groups. [a] Solitary Plasmacytoma of bone when there is single bone lesion, [b] Solitary Extramedullary plasmacytoma when there is single soft tissue lesion, [c] Multiple Solitary Plasmacytoma when there are Multiple sites of disease in bone, soft tissue or both. Extramedullary involvement with multiple myeloma is generally a manifestation of advanced disease.\textsuperscript{[2]} It occurs in 3 % cases of multiple myeloma which are also called as secondary plasmacytoma. There is a female preponderance of 3:1.\textsuperscript{[4]} We discuss the clinicoradiological evaluation, pathological confirmation and the management in our cases of Orbital plasmacytoma.

METHODS:

This is a retrospective observational and interventional case series of five patients from 2013 to 2019 at a tertiary eye care centre in India. Medical records were reviewed for patient information including demographics, clinical features, radiologic features, pathologic features and management strategy.

RESULTS:

Three patients (60 %) were diagnosed with orbital plasmacytoma and two (40 %) were diagnosed with conjunctival and orbital plasmacytoma. Male to female ratio was 2:1 (M = 4, F = 2) with a mean age of 51.8 years (range 20 – 70 years) at the time of presentation. Four were unilateral (80 %) and one was bilateral (20 %). Mean onset of symptoms was 14.1 days. All patients (100 %) underwent incisional biopsy. EBRT was given in four patients (Pre incisional biopsy EBRT was done in 2 (50 %) which was given earlier for systemic MM and 2 (50 %) post incisional biopsy EBRT). Three (60 %) patients in this
study were diagnosed with orbital plasmacytoma as a manifestation of multiple myeloma and two (40 %) were having solitary plasmacytoma. Incisional biopsies showed CD138 positivity in all patients. Two (40 %) patients were treated with a combination of chemotherapy and bone marrow transplantation; whereas, three (60 %) patients were treated with EBRT alone. One patient did not follow the treatment advice and was not investigated further after incisional biopsy. Among the treated ones, One patient (20 %) showed excellent response to treatment, one (20 %) showed good response to treatment (had <10 % plasma cells in Bone marrow aspiration), Two (40 %) showed partial response (had >50 % plasma cells in Bone marrow aspiration) and one (20 %) had poor response (had 80 % plasma cells in Bone marrow aspiration). 6 cases of Orbital plasmacytoma are discussed here in detail.

CASE 1

A 51 year old female presented to us with swelling of Right Eye (RE) lower lid since 20 days associated with loss of sensation of teeth on right side. Her Best corrected visual acuity (BCVA) was 6/6 in Both eyes (BE). Her ocular movements were full and free and there was no associated proptosis. RE had a ptosis of 2 mm. On palpation there was firm, tender lesion along right inferior orbital rim but posterior margin was not palpable. Retrobulbar resistance was present. CT scan showed punched out lesions of skull, mass involving maxillary sinus and temporal fossa which was suggestive of plasmacytoma associated with Multiple Myeloma (MM). Incision biopsy was done. Histopathology report showed tumor cells of plasmacytoid appearance, punched out appearance of tumor cells, plasmablasts suggestive of plasmacytoma. (Figure 1) Immunohistochemistry (IHC) was positive for CD138 and lambda light chain restriction. Ki67 labelling index was 30 - 40 %. Bone marrow biopsy showed < 10% plasma cells. Urinary Bence Jones protein was negative. Calcium was normal. Serum protein electrophoresis showed elevated gamma globulins and M-Band (25.1 %) in gamma region. Based on clinical, radiological and
Histopathological reports diagnosis of Extramedullary plasmacytoma with Multiple Myeloma was made. Patient was started on chemotherapy (Bortezomib, Doxorubicin and Dexamethasone) for four cycles with allogenic bone marrow transplantation. Post treatment, her BCVA was 6/6 in BE. There was no mass felt on palpation and no orbital mass was seen (Figure 2). Patient showed very good response to therapy.

Figure 1: A: RE Upper eyelid ptosis and lower eyelid fullness. B: Homogenous irregular mass seen inferotemporally extending to maxillary sinus and eroding inferior orbital margin in RE and homogenous mass superotemporally eroding the superior orbital margin. C: multiple punched out lesions.

Figure 2 : A: Post treatment picture shows normal contour of lower lid with no ptosis and CT Scan (B) shows complete resolution of mass
CASE 2

A 70 year male presented to us with swelling in the left eye since 15 days. His Best Corrected Visual Acuity was 6/6P in RE and 6/9P in LE. Ocular movements of Left eye (LE) were restricted in all gazes except inferiorly and the patient had significant diplopia. There was proptosis of 5mm by Hertle's Exophthalmometry and hypoglossus of 2mm. MRI Orbit with contrast was done which showed a well defined soft tissue mass of approximately 30 x 30 x 15 mm in superolateral aspect of the left orbit which was isointense on T1 and T2 and is causing destruction of the adjoining left frontal bone in roof of the left orbit with intracranial extension in left frontal lobe. CECT Orbits confirmed the erosion of adjacent roof and lateral wall of left orbit and left frontal bone compressing the superior surface of the left globe and abutting the superior rectus. A multilevel incisional biopsy was done which showed poorly cohesive plasmacytoid cells, bi to multinucleate cells with marked nuclear atypia and specky necrosis. IHC was positive for CD138 with Ki67 labelling index of 60 - 70 % suggestive of Orbital Plasmacytoma. PET CT scan showed increased uptake in the left orbit with foci of increased uptake in left humeral neck and D4 transverse process. Biopsy of left humeral head lesion also showed features of plasmacytoma. A systemic evaluation for multiple myeloma was negative. Bone marrow biopsy showed < 10 % plasma cells. The final diagnosis of Multifocal Plasmacytoma of Bone was made. Patient was given EBRT to left orbit, left humeral head and D4 vertebrae. 6 months later, there was no palpable mass clinically, the intracranial component has resolved and good bone remodelling was seen. The patient was monitored for signs of multiple myeloma. After 1 year of radiation, the bone remodelling has further increased. Intralesional steroid injection was given for the residual lesion in the sphenoid wing. There is a significant increase in the bone growth after 6 months of intralional injection. There is no activity seen on PET Bone scan so the patient is advised for a regular follow up of 6 monthly for 3 years and then annual follow up to investigate for multiple myeloma. It has been 2 years since the time of presentation and he is doing very well. (Figure 4).
A 61 year male who was a known case of multiple myeloma presented to us with complaints of double vision in LE since 15 days. Palliative radiotherapy to spine has been given to him elsewhere. BCVA was 6 / 6P in BE. Ocular movements were restricted in LE superior and lateral gazes with diplopia. There was proptosis of 8mm by Hertles Exophthalmometry. There was diffuse red superior bulbar conjunctival infiltrate involving superior epibulbar, superior fornix, tarsal conjunctiva and lacrimal gland. CT scan orbit
showed ill defined lesion eroding superior and temporal aspect of left orbit. Incisional biopsy was done. Histopathology showed sheets of plasmablasts and plasma cells. Mitoses average $8 / 10$ HPF (Figure 5). Bone marrow biopsy showed $>50\%$ plasma cells. Serum electrophoresis showed monoclonal band positivity. Serum IgG and lambda light chains was raised. Based on above findings diagnosis of Extramedullary plasmacytoma with Multiple Myeloma was made. Patient underwent Localized radiotherapy to left orbit. There was partial response to treatment.

![Figure 5: A: LE Dystopia and proptosis. B: Red diffuse infiltrative lesion involving superior epibulbar conjunctiva, fornix and tarsal conjunctiva. C: Homogenous irregular mass superiorly eroding superior orbital margin.](image)

**CASE 4**

A 57 year male who was known case of Left submandibular node plasmacytoma and right ethmoidal sinus myeloma status post chemotherapy and radiotherapy presented to us with watering and swelling of LE. BCVA was $6 / 6$ P in BE. In LE there was restriction of ocular motility in upgaze associated with diplopia. There was proptosis of $6$ mm by
Hertles Exophthalmometry. CT Scan orbit showed lesion involving left frontal bone and ethmoidal sinus with extensive bony erosion. Incisional biopsy was done. Histopathology report showed poorly cohesive plasmacytoid cells (Figure 6). IHC showed CD138 positive. Serum electrophoresis showed M-Band in Gamma region with raised kappa light chain. Based on above findings diagnosis of Extramedullary plasmacytoma with Multiple Myeloma was made. Patient underwent Localized radiotherapy to left orbit. There was partial response to treatment.

**Figure 6**: A: Unilateral telecanthus and ptosis of LE. B: Homogenous ill defined mass involving nose, ethmoid sinus and frontal lobe of brain

**CASE 5**: A 20 year male noticed swelling in inferior orbit 18 days back. BCVA was 6 / 6 in BE. Ocular motility was full and free. On palpation there was non mobile mass palpated in inferior orbit attached to the floor of orbit with mild warmth and tenderness which was confirmed on CT scan orbit. Chemosis was present in inferior tarsal conjunctiva. Incisional biopsy was done which was suggestive of solitary orbital plasmacytoma (Figure 7). Bone marrow biopsy showed > 80 % plasma cells. A thorough systemic evaluation for plasma cell dyscrasia was negative. Bone marrow transplantation was done but patient succumbed within one year of treatment. There was poor response to treatment.
A 74 year female presented to us with swelling above the left eyebrow since 1 month. On examination her BCVA was 6 / 9 in RE and 6 / 12 P in LE. Extraocular movements were limited in upgaze and there is a hypoglossus of 3 mm and associated diplopia. There was proptosis of 4 mm in LE by Hertles exophthalmometry. There was temporal fossa fullness with firm, non-tender, non-mobile, non-compressible mass in superotemporal quadrant. CT scan showed a mass which had triradiate lesion of size 34.7 x 23.8 x 28.3 mm. Provisional diagnosis of LE proptosis to rule out plasmacytoma, meningioma, eosinophilic granuloma and osteogenic sarcoma was made. She underwent multilevel transseptal incisional biopsy which showed patternless proliferation of plasmacytoid
cells. IHC was CD 138 positive, monoclonal cells with kappa light chains only and Ki 67 labelling index of 30 - 35 %. These were suggestive of extraskeletal plasmacytoma. The patient denied any form of further evaluation and treatment but is currently doing well.

DISCUSSION

According to the International Myeloma Working Group, the diagnosis of multiple myeloma should fulfill the following criteria: clonal bone marrow plasma cells e” 10 % or biopsy-proven bony or extramedullary plasmacytoma plus any one of the following myeloma defining events: end organ damage (hypercalcemia, renal insufficiency, anaemia, bone lesions), or any one or more of the following biomarkers of malignancy, a clonal bone marrow plasma cell percentage e” 60%, an involved: uninvolved serum free light chain ratio of e” 100, or >1 focal lesions by MRI. The criteria for the diagnosis of SEP include negative lymph node assessment, skeletal survey, bone marrow biopsy, and computed tomography. Bonavolonta et al reported plasmacytoma had a prevalence of 3% patients and accounted for <1 % of total orbital lesions. The cases reported here represent a variety of eye and adnexal locations of plasmacytomas. We found two cases involving conjunctiva, one case involving lacrimal gland, one involving maxillary sinus and another involving ethmoidal sinus along with orbital lesion. In our case series there was male preponderance of 4:1 which was different from the study done by Wang et al in 2018 where they had a female preponderance of 3:2. This difference may be because of the study population. In our series mean age of diagnosis was 51.8 years which was different from study done by Terenzi et al in 2012 which showed mean age of 70 years at diagnosis and only 3.4 % of cases are diagnosed between 35 - 44 years of age. This difference may be because of difference in sample size and range of age group of sample. In our series most of the patients presented with diplopia and proptosis which was acute or subacute in onset with good visual acuity. This was in contrast to study done by Wang et al in 2018 where patients presented with proptosis and decrease in vision which was
insidious in onset. The differences in demographic details with our study may be due to the sample size, the range of age group and the relatively early presentation to us much before the involvement of the optic nerve. Four cases were unilateral (80 %) and one was bilateral (20 %). In Cases 1, 3 and 4 the orbital plasmacytomas presented in conjunction with evidence of systemic multiple myeloma. Case 2 and 4 had Extramedullary Plasmacytoma. Case 2,3 and 5 are associated with adnexal involvement. Case 1 and 4 are associated with paranasal sinus involvement. Case 5 of 20 year male is the youngest reported case of solitary orbital plasmacytoma to the best of our knowledge. Darbari et al in 1972 reported youngest case of plasmacytoma at 30 years of age. Reported cases of orbital plasmacytoma predominantly originate in the superotemporal quadrant of the orbit. Our series support this finding, with three out of five cases of orbital plasmacytoma occurring in superior quadrant. The most common type of heavy chain found in MM are IgG and IgA. This correlates with our finding where most common type of heavy chain was IgG (60 %). In our case series we found two cases (40 %) had lambda chains, two (40 %) cases had kappa chains and one (10 %) did not have any light chains. This is in contrast to Burk et al in 2009 who wrote Kappa and lambda light chains were present in a significant number of patients, but neither were more likely to involve the orbit. In our series all SEP were arising from paranasal sinuses. This matches with the study done by Webb et al in 1962 where they mentioned that solitary extramedullary plasmacytoma (SEP) are often found in the upper respiratory tract, and possess the ability to invade the orbit from the surrounding sinuses. Multiple myeloma is generally treated with systemic chemotherapy and autologous stem cell transplantation where appropriate.
Key features of the previous reported cases are summarised in Table 1.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Presentation (years)</th>
<th>Sex</th>
<th>Prior Treatment</th>
<th>Quadrant Involvement</th>
<th>Associated with MM</th>
<th>Treatment given</th>
<th>Response to treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>51</td>
<td>F</td>
<td>Nil</td>
<td>Inferior</td>
<td>No</td>
<td>BMT+Chemo</td>
<td>Good</td>
</tr>
<tr>
<td>Case 2</td>
<td>70</td>
<td>M</td>
<td>Nil</td>
<td>Superotemporal</td>
<td>No</td>
<td>EBRT</td>
<td>Good</td>
</tr>
<tr>
<td>Case 3</td>
<td>61</td>
<td>M</td>
<td>RT</td>
<td>Superior with conjunctival and LG involvement</td>
<td>Yes</td>
<td>Local EBRT</td>
<td>Partial</td>
</tr>
<tr>
<td>Case 4</td>
<td>57</td>
<td>M</td>
<td>RT</td>
<td>Medial and Superomedial</td>
<td>Ycs</td>
<td>EBRT</td>
<td>Partial</td>
</tr>
<tr>
<td>Case 5</td>
<td>20</td>
<td>M</td>
<td>Nil</td>
<td>Infero temporal with conjunctival involvement</td>
<td>No</td>
<td>BMT</td>
<td>Poor</td>
</tr>
</tbody>
</table>

**Table 1: Clinical Summary of cases**

**CONCLUSION:**

We have observed in our study that patients with bone marrow biopsy having $\leq 10\%$ plasma cells had good response to treatment, those with $\leq 50\%$ showed partial response to treatment and those with $> 80\%$ showed poor response to treatment. Further study on their correlation will definitely help in prognosticating and managing these patients.

**REFERENCES**


INTRODUCTION:

Retinoblastoma (Rb) is an aggressive pediatric ocular malignancy that manifest covertly with leukocoria and threatens the survival of patients. Rb is predisposed primarily by genetic mutations in RB1 in one or more cells of the retina [1]. It may be triggered by the loss of function or mechanistic alterations of other genes by various chromosomal or mutational events [2]. The incidence of retinoblastoma is 1 in 18,000 live births [2], with about estimated 2000 children being diagnosed in India each year [3]. The tumor appears as a unifocal or multifocal yellow-white retinal mass with a feeding retinal artery and draining vein. There is often surrounding subretinal fluid, subretinal seeds, or vitreous seeds [4]. Management of a child with retinoblastoma involves a balance of patient life with globe salvage and ultimate visual potential. The current management strategies has evolved from enucleation, brachytherapy, focal therapy, cryotherapy, transpupillary thermotherapy, laser photocoagulation to advanced chemotherapy comprising of various delivery routes and chemotherapy protocols [5, 6]. However, enucleation continues to
remain as critical choice for advanced retinoblastoma with metastatic phenotype, particularly in Asia and Africa \(^7\).

Advanced Rb tumors demonstrate massive choroidal invasion \(^8\) and metastatic spread, primarily through optic nerve \(^9\) and sclera \(^10\), to regional lymph nodes, central nervous system (CNS) and bone marrow \(^11\) causing potent threat to vision and life. Clinically, to manage metastatic Rb tumors, a very intensive multimodality approach incorporating high dose chemotherapy regimens involving carboplatin, etoposide and cyclophosphamide followed by radiation and autologous stem cell therapy are currently being considered \(^12\). However, advanced tumors evolve during each chemotherapy cycle and develop resistance to anticancer therapeutics, diminishing the efforts of the clinical management procedures \(^13, 14\). Metastatic tumors acquire chemotherapy resistance through trans-differentiation initiated by the epithelial to mesenchymal transition (EMT) program in different cancers \(^15, 16\). EMT program begins with the loss of epithelial phenotypes by downregulation of E-cadherin and tight junction adhesion molecules. The differentiated cancer cells transit to mesenchymal phenotype with an invasive dedifferentiated characteristic, eventually acquiring chemo-drug resistance.

In the present study, we discovered key EMT genes that drive metastatic dissemination in advanced Rb tumors. We profiled EMT signatures using microarray in advanced and non advanced Rb tumors and found key mesenchymal transition factors like ZEB1, Twist & N-cadherin to be significantly upregulated in advanced Rb tumors. Using in-vitro systems, we further investigated the underlying mechanisms that trigger EMT genes to acquire metastatic phenotype in advanced Rb tumors.
METHODS:

CLINICAL SAMPLES

The study was conducted in accordance with the Declaration of Helsinki principles under a protocol approved by institutional ethics committee of Narayana Nethralaya (EC Ref no: C/2013/03/02). Informed written consents were received from all parents before inclusion in the study. Histology confirmed Rb tumors (n = 9) comprising of Group E and Group D of age range 0.2 - 4 years and pediatric controls (n = 2) of age range (0.2 - 0.3 years) were used for the miRNA and mRNA microarray study. The details of clinical samples including age, gender, laterality, tumor viability, clinical and histopathology details are mentioned in Table 1.

<table>
<thead>
<tr>
<th>ID</th>
<th>Sex</th>
<th>Laterality</th>
<th>Age at presentation</th>
<th>Clinical Risk</th>
<th>IHC Group</th>
<th>AJCC Staging</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>M</td>
<td>Bilateral</td>
<td>15 months</td>
<td>Advanced</td>
<td>Group E</td>
<td>cT3b</td>
</tr>
<tr>
<td>P2</td>
<td>F</td>
<td>Unilateral</td>
<td>20 months</td>
<td>Advanced</td>
<td>Group E</td>
<td>cT3b</td>
</tr>
<tr>
<td>P3</td>
<td>M</td>
<td>Unilateral</td>
<td>24 months</td>
<td>Advanced</td>
<td>Group E</td>
<td>cT3b</td>
</tr>
<tr>
<td>P4</td>
<td>F</td>
<td>Bilateral</td>
<td>4 months</td>
<td>Advanced</td>
<td>Group E</td>
<td>cT3b</td>
</tr>
<tr>
<td>P5</td>
<td>M</td>
<td>Bilateral</td>
<td>30 months</td>
<td>Advanced</td>
<td>Group E</td>
<td>cT3b</td>
</tr>
<tr>
<td>P6</td>
<td>F</td>
<td>Bilateral</td>
<td>21 months</td>
<td>Non-advanced</td>
<td>Group D</td>
<td>cT2b</td>
</tr>
<tr>
<td>P7</td>
<td>F</td>
<td>Unilateral</td>
<td>28 months</td>
<td>Non-advanced</td>
<td>Group D</td>
<td>cT2b</td>
</tr>
<tr>
<td>P8</td>
<td>M</td>
<td>Unilateral</td>
<td>20 months</td>
<td>Non-advanced</td>
<td>Group D</td>
<td>cT2b</td>
</tr>
<tr>
<td>P9</td>
<td>M</td>
<td>Unilateral</td>
<td>21 months</td>
<td>Non-advanced</td>
<td>Group D</td>
<td>cT2a</td>
</tr>
<tr>
<td>Control 1</td>
<td>F</td>
<td>NA</td>
<td>3 months</td>
<td>Cardiac Arrest (no ocular complications)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Control 2</td>
<td>F</td>
<td>NA</td>
<td>2 months</td>
<td>Multiple organ dysfunction (No ocular complications)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

RNA ISOLATION:

Total RNA isolation from retinoblastoma tumors and control pediatric retina samples were performed using Agilent Absolutely RNA miRNA kit (cat# 400814) according to manufacturer's instructions. Total RNA was extracted from retinoblastoma cell lines (WERI-Rb1) using Trizol reagent (Invitrogen, Carlsbad, CA) and purified through RNA
binding columns available with Agilent Absolutely RNA- miRNA kit (cat# 400814). We performed on-column DNase treatment at 37°C for 15 minutes, prior to elution. The total RNA purity was measured using Nano drop (ND-1000 UV-VIS Spectrophotometer) and the total RNA integrity for microarray was assessed using Agilent 2200 Tape Station (cat# G2964AA). The RNA quality was maintained consistent across samples with a RIN value > 6 for gene expression studies.

**TUMOR mRNA PROFILING:**

Total RNA was isolated from 9 Rb tumors and 2 control pediatric retina samples using Agilent Absolutely RNA miRNA kit (cat# 400814) according to manufacturer’s instructions. Twenty-five nanograms of RNA from Rb tumors and control pediatric retina samples were labelled with Cy3 dye using an Agilent Low Input Quick Amp Labelling Kit (p/n 5190-2305). Gene expression microarray analysis was performed using the Agilent SurePrint G3 Human GE 8 x 60K V2 Microarray and an Agilent SureScan Microarray scanner. The gene expression data were extracted using Agilent Feature Extraction Software (11.5.1.1) and analyzed using Agilent GeneSpring GX 13.1. The analysis was carried out using a t-test unpaired statistical method with Benjamini Hochberg FDR method.

**CELL LINES:**

WERI-Rb1 & Y79 retinoblastoma cell lines were obtained from American Type Culture Collection (ATCC, Manassas, VA). The cells were cultured in RPMI 1640 medium (Gibco, Cat #11875093), supplemented with 10 % FBS and 1 % Pen Strep (Penicillin – Streptomycin) and maintained at 37°C in a humidified atmosphere of 5 % CO2, with intermittent shaking in an upright T25 flask.
GENE EXPRESSION ANALYSIS:

Total RNA extracted for microarray from clinical subjects, were also used for RT PCR validation. RT-PCR was performed with Agilent Brilliant III Ultra-Fast RT-PCR reagent (cat# 600884), using Agilent AriaMX real time PCR instruments. Relative mRNA expression levels were quantified using the ∆∆C(t) method (34). For in-vitro assays, total RNA was isolated from cells using the Trizol reagent (Invitrogen, Carlsbad, CA) according to the manufacturer’s protocol. 1µg of RNA was reverse transcribed using Bio-Rad iScript cDNA synthesis kit (cat# 1708890) and quantitative real time PCR was performed using Kappa Sybr fast qPCR kit (cat# KK4601) using Bio-rad CFX96 system. Relative mRNA expression levels were quantified using the ∆∆C(t) method. Results were normalized to housekeeping human β-actin.

RESULTS:

ADVANCED RB TUMORS HAVE UNIQUE EMT SIGNATURES.

We identified distinct dysregulated gene clusters, implicating gross differences between advanced intraocular tumour defined as AJCC Stage [17] cT3 or IIRC [18] Group E tumour (6089 genes, P < 0.05, FC > 2) and non-advanced intraocular tumour defined as AJCC Stage cT2 or IIRC Group D (7695 genes, P < 0.05, FC > 2) compared to pediatric retina. Notably, EMT transcription factors like ZEB1, SNAI2 and Twist were significantly upregulated in advanced tumors. High expression of these EMT transcription factors are associated with tumorigenic progression in other cancer systems [19,20]. In addition to these findings, advanced Rb tumors demonstrated cadherin switching phenotype with high expression of N-cadherin and low expression of E-cadherin in tumor tissues, suggestive of EMT dissemination [21]. We speculate that advanced tumors maintain high expression of EMT to promote invasion and metastasis.
RB CELLS CONFER HIGH EMT PROGRAM AND METASTASIS

To extend our study of the consequences of RB1 downregulation in Rb tumors and its influence on EMT signatures, we overexpressed RB1 in Rb null Y79 and WERI-Rb1 cells. In real time gene expression assays, we found that Rb over expression decreased key EMT factors like ZEB1, Slug and N-cadherin in the immunoblot. However, Rb over expression increased E-cadherin expression indicating a halt in the EMT switch. We further confirmed the findings using RT-PCR that revealed a mesenchymal transition trend in control Rb null cells compared to Rb over expression. Our findings strongly suggest EMT as a modulator of mesenchymal phenotype to further promote invasion and migration.

DISCUSSION

The present study identifies RB1 as a previously unrecognized regulator of EMT transcription factors in Rb tumors. We provide proof-of-concept evidence that mesenchymal transition in advanced Rb is likely to be halted by ectopic expression of RB1. Our focus here has been mainly on intraocular advanced and non-advanced retinoblastoma tumors, but our findings can be extended to other cancer systems that have persistent EMT mediated metastatic dissemination.

We identified the balance between EMT driven metastasis in Rb tumors to be influenced by RB1 gene. Recent reports support our findings, further highlighting the importance of RB1 / EMT circuits in cancers. Advanced Rb tumors have high ZEB1 and Twist expression and these EMT TFs are master regulators of transition program and their oncogenic functions are widely studied in metastatic breast cancer, colon cancer and glioblastoma. During the EMT process, ZEB1 transcriptionally suppress the expression of its target genes, such as epithelial markers (E-cadherin) and correspondingly increasing the mesenchymal levels of vimentin and N-cadherin. Transcriptionally,
loss of E-cadherin is associated with upregulation of genes involved in mesenchymal transition like N-cadherin, Vimentin and transforming growth factor-β (TGFβ) [26]. Likewise, oncogenic activation of Twist along with SNAI1 can prevent cells from oncogene induced failsafe programs through RAS pathway [27]. We propose that key EMT drivers like ZEB1 and Twist acquires transcript stability due to the loss of function of RB1 gene in retinoblastoma.

As the Rb pathway is not druggable, an alternative approach is to mimic its function to understand RB1 regulated EMT circuits in Rb deficient cancers. This concept is further supported by our observations with ectopic expression RB1 in Y79 and WERI-Rb1 cells, that repress ZEB1 and Twist expression and its targets E-cadherin, N-cadherin and vimentin signaling cascade, inhibiting EMT transition and metastasis. In conclusion, our work reveals the mechanistic link between RB1 and EMT in advanced Rb tumors. Our study identifies RB1 as a potential target for EMT program and offers encouraging prospects for managing advanced retinoblastoma.

REFERENCES:


ABSTRACT

PURPOSE:

To compare the functional outcomes of retropupillary iris claw lenses (RPIC-IOL) and scleral fixated intraocular lenses (SFIOL) in children with large lens subluxations.

METHODS:

A randomized comparative study was conducted in 28 eyes of patients between 6-18 years of age having 9/7 clock hours lens subluxation. They were equally divided into Group A (RPIC-IOL implantation) and group B (Gore-Tex sutured SFIOL implantation). Primary outcome was improvement in best corrected visual acuity (BCVA) at 3 months. Secondary outcomes were assessment of IOL tilt, mean change in astigmatism at 3 months and median operating time.
RESULTS:

The difference in the mean post-operative BCVA between group A (0.63 ± 0.28 logMAR) and group B (0.54 ± 0.29 logMAR) was not statistically significant (p = 0.399). Significant IOL tilt was seen in 2 eyes in group A (14.2 %) and 4 eyes in group B (28.57 %) (p = 0.120). Mean change in astigmatism was 4.38 ± 5.9 D in group A and 4.91 ± 4.4 D in group B (p = 0.299). The median operating time was 40 minutes in group A and 90 minutes in group B (p < 0.001). No significant posterior segment complications were seen in either technique.

CONCLUSION:

Our study shows that both procedures have comparable visual outcomes. RPIC-IOL implantation was relatively quick and needed lesser manipulation. Hence, we recommend it in cases with high risk of retinal detachment.

KEYWORDS:
Subluxated lens, ectopia lentis, Gore-Tex, scleral fixed lens, iris claw lens, SFIOL

INTRODUCTION

Lens subluxation in children is a challenging problem. It can induce significant astigmatism and high refractive errors leading to amblyopia and thereby hindering early visual rehabilitation.

Management of subluxated lenses varies from optical correction using spectacles / contact lenses in low grades of subluxation to lens removal and intraocular lens (IOL) implantation in higher grades. “In-the-bag” placement of IOL with Cionni ring is the ideal method in cases of mild to moderate subluxations. However, in cases with large subluxations, a pars plana lensectomy-vitrectomy followed by the management of resultant aphakia is recommended. The treatment options available are Scleral Fixated
IOLs (SFIOLs)-sutured or sutureless, Anterior chamber IOLs (ACIOLs) and Iris claw IOLs which can be placed in the posterior chamber (Retropupillary) or in the anterior chamber. Even though ACIOLs are surgically easier to implant and modern-day open loop ACIOLs have proved to be safe in few studies in children, their use may be complicated by uveitis, hyphaema, glaucoma and corneal decompensation over long term.\textsuperscript{1,2} Therefore, they are not widely accepted in children.

SFIOLs have the advantage of the lens being placed in a more physiological position. The technique of sutured SFIOL has evolved over time, beginning with the use of 10-0 prolene which was complicated by suture degradation and breakage\textsuperscript{3} followed by use of 9-0 prolene which has a better safety profile. Currently, 8-0 Gore-Tex (polytetrafluoroethylene) which has greater tensile strength is being used and has shown relatively good results in adult eyes.\textsuperscript{4,5,6} However, there is paucity of studies documenting its safety profile in pediatric eyes.

In recent years, Sutureless Scleral Tunnel IOLs (SSTIOLs) have gained popularity. This technique eliminates the suture related complications of SFIOLs while maintaining advantages over ACIOLs. Also, smaller incision gives lesser astigmatism, globe stability and less frequent globe collapse intraoperatively. However, they are less suitable for cases with horizontal limbus-limbus diameter > 12 mm. Low scleral rigidity in pediatric eyes makes this surgery more difficult and challenging.

Retropupillary Iris Claw IOLs (RPIC-IOLs) are technically simpler than SFIOLs and avoid corneal complications of ACIOLs. However, they may be associated with problems like spontaneous disenclavation and pupil ovalization.\textsuperscript{7,8}

Currently there is no consensus as to which of these techniques is best for management of large subluxations in children. Hence, we carried out this study to assess and compare the visual outcomes and stability of RPIC-IOL and sutured SFIOL (using Gore-Tex) in
children. We have also addressed the questionable safety profile of Gore-Tex assisted SFIOL in pediatric eyes as there is paucity of similar studies in literature.

MATERIAL AND METHODS

We conducted a randomized comparative interventional study in a tertiary eye care centre, registered with Clinical trial registry – India (CTRI/2020/02/023156). Approval was taken from the Institutional Ethics Committee. Research adhered to the tenets of the Declaration of Helsinki. 28 eyes of children in age group 6 - 18 years with crystalline lens subluxation > 7 clock hours (ectopia lentis) were enrolled in the study after taking informed consent and were divided into two groups of 14 eyes each. Group A underwent retropupillary iris claw lens implantation (RPIC-IOL group) and Group B underwent sutured scleral fixated intraocular lens implantation using 8-0 Gore-Tex (SFIOL group). For allocation of the participants, a computer-generated list of random numbers was used. Cases with gross iris abnormality, glaucoma, uveitis, gross anterior segment trauma/traumatic mydriasis and posterior segment abnormalities were excluded.

A thorough pre-operative ophthalmic evaluation was performed including best corrected visual acuity (BCVA) using Snellen chart, retinoscopy (wherever possible), slit lamp examination, automated keratometry (UNICOS URK-700), endothelial cell count (SP-200P), intraocular pressure (IOP) measurement (SHIN-NIPPON NCT-10) and dilated posterior segment assessment. Contact biometry was done by SW-1000AP using SRK a! formula. Ultrasound B scan (APPASWAMY MARVELL-II) was done wherever fundus evaluation could not be performed. Pediatric review was done to rule out associated syndromes. Echocardiography was done and cardiology opinion was sought wherever needed. IOL used in group A was iris claw lens [Irisfix, Model No J-IF54, overall diameter of 8.50 mm, optic diameter of 5.40 mm with an estimated A constant of 117.4 for posterior chamber]. In group B, SFIOL [Akreos A060 (Bausch and Lomb), overall diameter of 11 mm, optic
diameter of 6 mm with an estimated A constant of 118.0] was used. The target refraction was emmetropia.

SURGICAL TECHNIQUE

All surgeries were performed by same surgeon using Alcon Centurion machine under general anesthesia in younger children and local anesthesia in older children. Time taken for each procedure was noted.

GROUP A (RETROPUPILLARY IRIS CLAW LENS)

A 23 G infusion cannula was placed 3 mm behind the limbus infero-temporally. Pars plana lensectomy-vitrectomy was done using 23 G vitrectomy cutter. Paracentesis at 10 o’clock and 2 o’clock positions were made. A corneo-scleral section of 4.5 mm was made.

FIGURE 1: SURGICAL STEPS OF RPIC-IOL IMPLANTATION

A: Corneal markings being made 180° apart; B: Pars-plana lensectomy-vitrectomy being done; C: RPIC-IOL showing claw (black arrow) for iris tissue enclavation; D: Insertion of IOL into anterior chamber; E: IOL being slipped into posterior chamber and enclaved in mid-peripheral iris; F: Well-centered IOL with patent peripheral iridectomy at the end of surgery
The iris claw lens was inserted vertically in the anterior chamber and was nudged to horizontal position. It was slipped posteriorly with lens holding forceps. The midperipheral iris was enclaved at 3 o’clock and 9 o’clock positions 180º apart using a Sinskey hook one after the other. Peripheral iridectomy was done and the section was closed with 10-0 vicryl followed by sclerostomy closure with 8-0 vicryl.

**GROUP B (SUTURED SCLERAL FIXATED INTRAOCULAR LENS):**

Limbus was marked at two points in the horizontal plane 180º apart using toric lens marker. Nasal and temporal peritomies were done. Four sclerotomies were made (2 on each side) 3 mm behind the limbus and 5 mm apart using 23 G trocar. Pars plana lensectomy-vitrectomy was done. A clear corneal incision of 3.2 mm was made. The Gore-Tex suture was cut into half and each end was threaded through the two eyelets of

**FIGURE 2: SURGICAL STEPS OF SFIOL IMPLANTATION**

A: Corneal markings being made 1800 apart; B: Creation of sclerotomies 3 mm from limbus and 5 mm apart followed by pars-plana lensectomy-vitrectomy; C: SFIOL with four eyelets; D: Gore-Tex being threaded through IOL eyelets; E: Insertion of SFIOL into anterior chamber after pulling out Gore-Tex threads through corresponding sclerotomies; F: Well-centered IOL after surgery
the SFIOL on either side. The suture ends were then passed into the anterior chamber and pulsed out of the corresponding sclerotomy using 23 G intravitreal forceps. The clear corneal incision was enlarged to 4.0 mm. The IOL was folded and introduced into the anterior chamber using Kelman-McPherson forceps. The sutures were tied using a 3-1-1 technique after ensuring IOL centration by adjusting the tension of sutures on either side. The knots were trimmed and buried into one of the sclerotomies. The sclerotomies were sutured with 8-0 vicryl and the corneal section with 10-0 vicryl. The conjunctiva was closed (Figure 2).

Post-operative analysis was done at day 1, 1 week, 1 month, 6 weeks, 3 months. IOL tilt was assessed by UBM by method described by Loya et al (>100 microns tilt with reference to iris plane was considered as significant).9

**POST-OPERATIVE PERIOD**

All patients received a 5-day course of systemic antibiotics (Amoxycillin 30 mg/kg/day in three divided doses) along with topical Prednisolone 1%, topical Tobramycin (0.3%) and Homatropine (2%). Timolol 0.5% eye drops and oral Acetazolamide (15 mg/kg in three divided doses) were prescribed in cases where the post-operative intraocular pressures were found to be high.

**RESULTS**

The mean age was 9.57 ± 4.13 years in group A and 9.64 ± 4.09 years in Group B. The cause of subluxation in Group A was high myopia in 8 cases (57.14%), Homocystinuria in 1 case (7.14%), Marfan’s syndrome in 1 case (7.14%) and idiopathic in 4 cases (28.57%) whereas in group B it was high myopia in 3 cases (21.43%), Homocystinuria in 1 case (7.14%), Marfan’s syndrome in 2 cases (14.29%) and idiopathic in 8 cases (57.14%). In Group A, the axial length (AL) ranged from 21.6 - 28.8 mm with a mean of 25.25 ± 2.44 mm whereas in Group B, AL ranged from 20.75 - 27.64 mm with a mean of 24.21 ± 2.27 mm (p = 0.256).
Both the groups showed a significant change in best corrected visual acuity (BCVA) postoperatively at 3 months. In group A, the mean pre-operative BCVA was 0.91 ± 0.42 logMAR and mean post-operative BCVA at 3 months was 0.63 ± 0.28 logMAR (p = 0.025). In group B, the mean pre-operative BCVA was 0.98 ± 0.38 and mean post-operative BCVA at 3 months was 0.54 ± 0.29 logMAR (p = 0.003). In our study, the improvement in BCVA at 3 months was better in the SFIOI group (0.44 ± 0.45 logMAR) as compared to the RPIC-IOL group (0.28 ± 0.41 logMAR) but this difference was not statistically significant (p = 0.322).

In group A, the mean pre-operative astigmatism was -5.85 ± 5.38 D and mean post-operative astigmatism at 3 months was -1.38 ± 1.65 D (p = 0.044). In Group B, mean pre-operative astigmatism was -7.05 ± 4.13 D (p = 0.572) and mean post-operative astigmatism at 3 months was -2.11 ± 1.99 D (p = 0.004). However, the difference between the two groups at 3 months was not statistically significant (p = 0.300).

The median operating time was 40 minutes in Group A and 90 minutes in Group B (values were not normally distributed, so median was taken). The difference in the two groups was statistically significant (p = < 0.001).

IOL centration was evaluated in all patients by slit lamp examination at every visit. The decentration was measured in millimeters from the margin of the pupil in undilated state. At 3 months follow-up, IOL decentration was seen in 1 eye in group A (1 mm) and in 3 eyes in Group B (1 mm, 1.2 mm, 1.5 mm). Since the visual acuity was good and it was evident only on pupillary dilatation, no surgical intervention was done. At 1-year follow-up, there was no further increase in decentration in the above eyes or in the eyes which had no decentration at 3 months.

A significant IOL tilt was seen in 2 eyes (14.29 %) of group A and in 4 eyes (28.57 %) of group B. The difference was not statistically significant between the groups (p = 0.120).

In group A, the mean LogMAR BCVA in eyes with significant tilt was 0.65 ± 0.21 and in
eyes without significant tilt was 0.65 ± 0.29 (p = 0.984). In Group B, the mean LogMAR BCVA in eyes with significant tilt was 0.5 ± 0.36 and in eyes without significant tilt was 0.63 ± 0.19 (p = 0.428). Overall, the mean BCVA in eyes with significant tilt was 0.53 ± 0.32 logMAR and in eyes without significant tilt was 0.65 ± 0.26 logMAR. This difference was not statistically significant (p = 0.334).

The mean postoperative astigmatism in eyes with significant tilt (both group A and B) was -2.33 ± 2.37 D and in eyes without significant tilt was -1.56 ± 1.57 D. This difference was not statistically significant (p = 0.326).

The post-operative intraocular pressure (IOP) was measured at 1 week, 1 month and 3 months. The difference between the two groups at each visit was not statistically significant. 1 eye in group A and 3 eyes in group B developed immediate post-operative hypotony which resolved by 2 weeks on medical management. 1 eye in group A had small lens fragment drop and developed high IOP which was uncontrolled on oral as well as topical antiglaucoma medications. Complete vitrectomy and removal of lens material was done at second stage after which IOP was normalized.

In 1 eye with significant cataractous changes fundus could not be visualized. The ultrasound B-scan of this eye was anechoic. 1 eye in group B had lattice degeneration for which laser was done pre-operatively. Fundus evaluation was normal in all cases till last follow-up.

**DISCUSSION**

Management of large lens subluxation in children continues to be a perplexing problem for pediatric ophthalmologists. In-the-bag placement of IOL with the aid of Cionni ring remains most acceptable option but its technically challenging.\(^\text{10}\) In cases where it is not feasible, lens extraction can be done with the management of resultant aphakia. The choice of IOL to be implanted is the next challenge as early visual rehabilitation with minimal complications is the ultimate goal in children.
A wide variety of IOLs and various techniques of their implantation have been described in literature with associated merits and demerits of each. ACIOLs are technically easier to implant but they are not free of complications. SFIOL is a time-tested option for eyes with inadequate capsular support due to their placement in a more physiological position. However, it is also not without complications. Retinal detachment, IOL tilt, vitreous or suprachoroidal hemorrhage, endophthalmitis and suture erosion / breakage have all been reported. Iris claw lenses avoid potential complications of ACIOLs and SFIOLs. However, they may be associated with spontaneous disenclavation, iris chaffing / atrophy, pigment dispersion, hyphaema and pupil ovalization.

Many studies have evaluated 10-0 polypropylene for SFIOL in children and have reported IOL dislocation secondary to suture breakage. Use of thicker sutures like 9-0 prolene is considered a better alternative for scleral fixation in children due to its better safety profile. Current literature supports superiority of 8-0 Gore-Tex over 9-0 prolene for suturing SFIOL because of its greater tensile strength, high visibility due to its white color, minimal inflammatory response, minimal memory and easy manipulation. Khan et al did SFIOL (Akreos) implantation using 7-0 Gore-Tex suture in 85 eyes and there was no reported case of suture breakage during follow-up. Other studies have shown similar safety profile in adult eyes. However, there is lack of documentation of its safety profile and outcomes in pediatric eyes. Since, it is difficult to manage low scleral rigidity in pediatric eye, the technicality required in every step of SFIOL implantation using Gore-Tex has not been described till date. Also, there is lack of comparative data between RPIC-IOL and sutured SFIOL in pediatric eyes. This study highlights the comparison of functional outcomes in both the procedures and addresses the technical and safety concerns of Gore-Tex assisted SFIOL in children.

In our study, there was a statistically significant improvement in the mean BCVA in both the groups post-operatively. SFIOL group showed a better visual outcome at post-operative 3 months compared to RPIC-IOL group, but it was not statistically significant.
Rashad et al reported a mean BCVA of $0.51 \pm 0.25$ logMAR in the RPIC-IOL group and $0.42 \pm 0.16$ logMAR in the SFIOL group at last follow-up ($p = 0.152$). Their mean BCVA at all post-operative visits was better in the SFIOL group which is comparable to our study. Han Zhang et al reported a mean BCVA of $0.55 \pm 0.22$ logMAR in the RPIC-IOL group and $0.53 \pm 0.19$ logMAR in the SFIOL group ($p = 0.249$). However, both these studies have been done in adult eyes (54 ± 11 years in the former; 15-75 years in the latter).

Visual recovery was found to be earlier in RPIC-IOL group (mean UCVA was better in group A when compared to group B at post-operative day 1). This could be attributed to a shorter median operating time as implantation of an iris claw lens is technically simpler with fewer steps as compared to group B where, surgeon faced difficulty due to low scleral rigidity. Since there were four suture ends, suture orientation and entanglement during SFIOL placement were encountered in few cases. The sclerotomies were created using 23 G trocars and thus they all had to be sutured at the end of the surgery. This also contributed to a longer operating time in Group B. Rashad et al has also reported an early visual recovery in their RPIC-IOL group which they attributed to the uncomplicated nature of the surgery and a shorter operating time. Amblyopia was a limiting factor for early visual recovery in 7 eyes in group A and 3 eyes in group B of our study.

The mean post-operative spherical equivalent (SE) showed a hypermetropic trend in group A and myopic trend in group B which correlates well with study by Botsford et al who did SFIOL implantation using Gore-Tex in 31 eyes and reported a post-operative myopic trend. However, this study was done in adult eyes. Rastogi et al reported mean post-operative SE -2.07 ± 0.91 with iris claw lens in 14 eyes between 8-7 years of age. However, the technique used to insert the IOL in the study was through corneo-scleral tunnel. Also, there is no mention of pre-operative and post-operative keratometric data. Gonnerman et al reported mean post-operative SE of $0.00 \pm 1.21$ diopters (D) (range “2.25 to + 4.50 D) with iris claw lens which they implanted through scleral tunnel incision.
In our study, 2 patients in group A and 4 patients in group B were noted to have a significant IOL tilt. However, the difference was not statistically significant (p = 0.12). Also, the mean difference in BCVA in eyes with and without significant tilt was not statistically significant (p = 0.334). Mahajan et al reported 2 cases of IOL tilt in RPIC-IOL group and 4 cases in SFIOL group. However, the method for IOL tilt measurement and its significance value is not described. Additionally, they did not compare the BCVA or astigmatism in eyes with and without significant tilt. Patel et al did SFIOL implantation with Gore-Tex in 49 eyes and reported IOL tilt in 2 eyes post-operatively but they did not quantify the amount of tilt.

The mean change in astigmatism was statistically significant in each group and was comparable in between the groups at last follow-up. Our study showed a myopic trend in post-operative astigmatism in both the groups. Our results are not consistent with other studies. Han et al reported hyperopic astigmatism of 0.84 ± 0.53 D in sutured iris fixated group and 1.23 ± 0.70 D in SFIOL group. Botsford et al reported a mean astigmatism of 1.65 ± 1.45 D with SFIOL using Gore-Tex. A smaller incision helps limit the post-operative astigmatism to an acceptable range. The incision required to insert the non-foldable RPIC-IOL is 4.5 mm which is larger than that required for foldable SFIOL (4.0 mm). But post-operatively, eyes with IOL tilt were more in the SFIOL group compared to RPIC-IOL group resulting in higher astigmatism in the former and negating the benefit of a small incision. Since there is paucity of literature on Gore-Tex sutured SFIOL implantation in children, this data needs more documentation in future studies.

1 case in group A had intraoperative small lens fragment drop with high IOP uncontrolled with topical and oral anti glaucoma medications on follow-up for which pars plana vitrectomy was done in second stage. The post-operative period was uneventful. None of our cases had retinal detachment, pseudophacodonesis or IOL dislocation. No sclerotomy related complications were seen as all were sutured with 8-0 vicryl. The most common post-operative complication in group A was pupil ovalization which had no effect on the
final BCVA or pupillary dilation. The most common post-operative complication in group B was IOL tilt. This could be attributed to not so precise markings in these eyes. Authors would like to highlight that meticulous marking is of utmost importance in achieving good IOL centration and stability. This especially becomes challenging in eyes under general anesthesia where globe tends to diverge. 22 This coupled with multiple sclerotomies and post-vitrectomy hypotony makes globe handling difficult. We recommend use of smaller gauge instruments to reduce the need for additional suturing and to minimize sclerotomy site leakage and thus hypotony. For the ease of instrument transfer and suture passage, valved cannulas can also be used. Gore-Tex could be a stronger & safer option in pediatric eyes especially in non-Marfanoid cases. However, this study is limited by a small sample size. More studies with larger sample size are needed to support this.

CONCLUSION

Both RPIC-IOL and SFIOL respect the anterior segment anatomy and corneal endothelium as they are placed behind the iris plane. We conclude that both techniques provide good visual rehabilitation and IOL stability in children with large lens subluxations. RPIC-IOL implantation is technically simple and needs significantly lesser intraoperative manipulation. Hence, we recommend it in subjects with high risk of retinal detachment like Marfan’s syndrome, high myopia and presence of peripheral retinal degenerations.

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Insights Into Pediatric Pythium Keratitis - A Clinical Case Series From Tertiary Eye Care Center

Dr. Bharat Gurnani

AIM

To study demographics, risk factors, clinical challenges, and treatment outcomes in managing Pediatric Pythium Keratitis.

METHODS

Retrospective analysis of culture-proven Pediatric Pythium subjects was performed from October 2017 to December 2019. Demographic details, risk factors, microbiological details, clinical course, treatment, and visual outcome were analysed in detail.

RESULTS

A total of 7 patients were analyzed. The mean age was 11.42 ± 1.2 years. Presenting visual acuity ranged from 20/20 to perception of light (PL+). The most common predisposing risk factors were mud injury in 3 (42.85 %) patients, stick injury in 2 (28.57 %) patients, and 1 (14.28 %) bath in pond water. The most common clinical presentation was subepithelial infiltrate, tentacular projections, and peripheral furrowing
in 4 (57.14 %) patients each, and 3 (42.85 %) patients showed stromal infiltrate. The microbiological diagnosis was based on growth on blood agar culture, and confirmation was based on vesicles with zoospore formation by the leaf incarnation method. Based on diagnostic algorithm and culture results, patients were treated with antifungals 5 % Natamycin or 1 % Itraconazole/Voriconazole and 0.2 % Linezolid and 1 % Azithromycin. 2 patients healed with medical management. Three underwent Therapeutic keratoplasty (TPK), 1 had Repeat TPK. Three underwent Optical Penetrating Keratoplasty (OPK), and two were awaiting optical PK. 2 had reinfection. Two improved to 20/30, and 5 patients had final VA ranging from 20/200-20/1200. Globe salvage was 100%.

CONCLUSION

Pediatric Pythium Keratitis is a rare entity. Non-resolving fungal keratitis should be kept as a differential diagnosis. Prompt diagnosis, clinical awareness, and specific treatment options are needed for managing this devastating corneal entity.

KEYWORDS

Pediatric Pythium Keratitis, Pythium insidiosum, Tentacles, Leaf Incarnation

INTRODUCTION

Infectious keratitis is a significant cause of ocular comorbidity in the pediatric age group. If not treated aggressively, it can lead to irreversible visual sequelae like corneal opacity, amblyopia, and phthisis bulbi. [1] The variety of microbial keratitis in pediatric cases includes fungal, bacterial, and viral keratitis. [2] Although microbial keratitis is not very common in the pediatric age group, a detailed analysis from southern California reported an 11 % prevalence of pediatric keratitis among all microbial keratitis cases. [3] Recently pediatric keratitis has seen an emergence of a new world species in the form of Pythium insidiosum keratitis, which is rarely reported. Pythium keratitis closely mimics fungal
keratitis clinically and is difficult to manage devastating ocular pathology. Pythium Insidiosum is Oomycete and belongs to Phylum Straminipila, Class Oomycetes, Order Pythiales, and Family Pythiaceae. [4] Previously, it was considered fungus until histopathological analysis revealed that the cytoplasmic membrane does not contain ergosterol, and the organism multiplies through asexual reproduction by forming sporangia containing zoospores as well. [5] The first report of this rare entity dates back to Thailand, where it was initially considered endemic; since then it numerous reports have emerged from Australia [6], China [7], Israel [8], and India [9]. The various forms of Pythium reported are ocular, vascular, cutaneous/subcutaneous, and disseminated. On slit-lamp examination, Pythium closely resembles fungal keratitis. Still, few important differentiating features which can clinch the diagnosis are stromal infiltrate with hyphated edges, tentacular projections, peripheral furrowing, and thick cotton wool-like infiltrate. The treatment options available are antifungal drugs (5% Natamycin, 1% Itraconazole, and 1 % Voriconazole) antibiotics, cyanoacrylate glue for melt, and therapeutic keratoplasty. [10]

As per the detailed literature review, this is the first case series on pediatric Pythium keratitis. This retrospective analysis aimed to highlight the clinico microbiological profile of a case series of pediatric patients of Pythium keratitis presenting between October 2017 to December 2019 at our tertiary eye care referral center in South India. This paper also details the risk factors, demographic profile, clinical features, microbiological profile, management, and treatment outcomes. We have also aimed to propose a diagnostic and treatment flowchart for Pythium cases, which will help all the ophthalmologists while dealing with this virulent infection.
METHODOLOGY

This was a retrospective observational study done for 27 months from October 2017 to December 2019 at our tertiary eye care hospital in South India. The study complied with the tenets of the Declaration of Helsinki. The study approval was obtained from the Institutional Review Board (IRB) of the Institutional Ethical Committee (IEC). The data of all individual cases and microbiology records of all culture-positive Pediatric Pythium insidiosum patients were obtained from Electronic Medical Records (EMR) data system [Fig. 1 Diagnostic Flowchart].

The data were evaluated for demographic details, a time lag of presentation, risk factors, clinical features, microbiological profile, medical and surgical treatment response, and visual outcome. The study's inclusion criteria were: (1) All culture-positive Pediatric Pythium cases up to 18 years of age and (2) Post keratoplasty button culture-positive cases. The criteria for exclusions were: (1) Incomplete medical records and (2) Absence of laboratory investigations despite clinical suspicion. The demographic, risk factors, uncorrected and best-corrected visual acuity by Snellen chart, detailed anterior and posterior segments findings along with microbiological results were retrieved from the...
medical case records. At our center, we routinely perform corneal scrapings under topical anesthesia using 0.5 % proparacaine. These specimens include scrapings for smear examination (Grams stain and 10 % potassium hydroxide wet mount) along with subsequent sequential scraping for culture on blood agar and potato dextrose agar. Additionally, zoospore formation of Pythium insidiosum was also confirmed by the incubated carnation leaf method. The treatment was initiated when clinical and microbiological results were available. Pythium hyphae closely mimic fungal hyphae on smear examination, so before the culture results were available, the eyes with positive smears having hyphae were treated with hourly topical antifungals in the form of 5 % Natamycin suspension, 1 % Itraconazole, or 1 % Voriconazole. If the ulcer size was less than 4 mm x 4 mm, the eyes were treated with single antifungal in the form of 5% Natamycin hourly suspension, and if the ulcer size was more than 4 x 4 mm, they were treated with a dual drug therapy of either 5 % natamycin and 1 % Itraconazole hourly or 5% Natamycin and 1% Voriconazole hourly during waking hours. After five days, when the culture results were available, the flat, feathery colorless colony growth of the Pythium species on the blood agar prompted the possibility of Pythium, which was further confirmed by zoospore formation on an incubated carnation leaf. If the culture result was positive for Pythiuminsidiosum, the patients were treated with topical Linezolid 0.2% hourly if the ulcer size was less than 4 x 4 mm and topical Linezolid 0.2 % and Azithromycin 1 % combination if the ulcer was more than 4 x 4 mm during waking hours. Patients who had poor response despite adequate and appropriate antimicrobial therapy, corneal perforation, and non-resolving ulcers involving limbus were subjected to Therapeutic keratoplasty (TPK). The excised corneal button was also cultured on blood agar and potato dextrose agar and was processed for species identification. Postoperatively, all eyes were treated with topical Linezolid 0.2 % alone or topical Linezolid 0.2% and Azithromycin 1% combination on an hourly basis for a minimum period of 3 weeks based on clinical picture preoperatively. Moreover, if the culture was positive, but button culture was negative post keratoplasty, patients were started on steroids and antibiotic
combination in the form of 0.1% Dexamethasone or 1% Prednisolone with 0.5% Moxifloxacin after a minimum of 2 weeks of anti-Pythium therapy. However, if the culture was positive and button culture was also positive post keratoplasty, patients were started on steroids and antibiotic combination in the form of 0.1 % Dexamethasone or 1% Prednisolone with 0.5 % Moxifloxacin after a minimum of 3 weeks of anti-Pythium therapy. On follow-up, the steroids were started in tapering doses under close observation only if there was no recurrence of infection postoperatively. Patients continued to be on a maintenance dose of anti-Pythium therapy for at least four weeks after initiation of topical steroids. They were closely monitored for the development of re-infection. Those patients with an active infection in the form of graft infiltrate or melt are taken for repeat TPK. Graft infections after the second TPK were conservatively treated with lateral tarsorrhaphy.

RESULTS

A total of 2039 ulcers presented to us during the study period, out of which 1003 were culture negative, 847 were positive for fungus, 161 were bacterial, and 30 were positive for Pythium. Out of 30, 7 pediatric Pythium Keratitis subjects were analyzed during the study period. The mean age of the subjects was 11.42 ± 1.2 years, with a range of 7-18 years. The male: female ratio was 4:3. The right eye was involved in 5 (71.42%) patients, and the left eye was involved in 2 (28.57%) patients. All subjects were students. The most common risk factors were Mud injury in 3 patients, stick injury in 2 patients, and no trauma history in 2 patients. The average time taken from the onset of symptoms to the presentation was nine days. There was a presentation lag of < 5 days in 2 (28.57%) patients, 6-14 days in 4 (57.14%) patients and >14 days in 1 (14.28%) patients. Visual acuity at presentation ranged from 20/20 to PL+ [Table 1a]. Two subjects had visual acuity in the range of 20/20-20/200, 4 had 20/240-20/1200, and 1 had HM+ to PL+. Based on severity grading of ulcers, a total of 2 (28.57 %) were mild ulcers, 3 (43.85 %) were moderate, and 2 (28.57 %) fell into the severe category. The mean size of the ulcer
was 32.04 ± 1.2 mm² with a range of 48.1 mm². The clinical features were patchy subepithelial dot-like infiltrates in 4 (57.14%) patients, tentacular projection in 4 (57.14%), stromal infiltrate with feathery margins in 3 (42.85%), subtotal infiltrate with peripheral furrowing in 4 (57.14%), thick endothelial plaque in 3 (26.6%), and total corneal melt in 2 (28.57%) patients. Hypopyon and anterior chamber exudates were present in 3 (42.85%) patients [Table 1b] [Fig. 2a-d].

Healing margins were present in 3 (23.3%) out of 7 patients. The smear examination revealed slender hyaline hyphae of all patients on 10% KOH wet mount [Fig. 3a]. The hyphae are studded with numerous vesicles. The culture results after five days showed a flat, feathery, colorless colony of P. insidiosum grow at 37°C on 5% sheep blood agar [Fig. 3b, c]. All seven patients were positive for Pythium in their first corneal scraping, 3 (42.85%) patients tested positive on repeat scraping, and 4 (17.8%) patients again tested positive when the corneal button removed for keratoplasty turned positive for Pythium. Additionally, Pythium identification was also confirmed by Zoospore formation.
on incubated carnation leaf [Fig. 3d]. Before culture results were available, 5 (71.42 %) patients were treated with topical 5% Natamycin suspension hourly alone, 2 (50%) were treated with topical 5% Natamycin and 1% Voriconazole hourly eye drops. After culture results, all seven patients were treated with topical 0.2% Linezolid and in 5 (71.42 %) patients were treated with topical 0.2% Linezolid and 1% Azithromycin eye drops combination [Table 2a, 2b].

A total of 3 (42.85 %) patients healed with medical treatment, 4 (57.14%) underwent TPK. The graft reinfection was seen in 2 (28.57%), and both patients underwent repeat TPK [Fig. 4a-d]. The mean time from presentation to TPK was seven days. The time for recurrence after TPK varied from 0 to 23 days with a means of 14.3 days. Adjunctive measures like cyanoacrylate glue for perforation in 2 patients eventually improved with medical management. The average time of occurrence of perforation was ten days after the initial presentation. The most common complication was choroidal detachment in 2
(28.57%) patients followed by graft reinfection in 1 (14.28%) patients, and none of the patients had endophthalmitis or underwent evisceration - [AQ1 Table 3].

Among the medically healed and TPK group, the average time taken for the presentation was 3.4 days in the former and 12.16 days in the latter. The final visual acuity was 20/20 20/200 in 3 (42.85%) patients, 20/240 20/1200 in 3 (42.85 %) patients, and hand movement to a positive perception of light in 1 patient.

DISCUSSION

Pythium keratitis is a devastating ocular entity that closely mimics fungal keratitis. P. insidiosum is an oomycete that morphologically exhibits features of branching, sparsely septate or aseptate filaments, and causes severe vision-threatening keratitis. Recently there have been numerous ocular and systemic reports of Pythium from all over the world. In this case series, we have described clinicopathological and microbiological details of pediatric Pythium cases, which as per the detailed literature review, is the first clinical case series of pediatric Pythium cases.

Our first case was a nine-year-old boy who had a presenting visual acuity of 20/40 with
a two-third depth 4 x 3 mm creamy white infiltrate in the right eye. The culture report was negative; hence the patient was managed with antifungals initially. The child underwent TPK 45 days later, post which button culture was positive. He developed a graft infection 15 days later, for which he was planned for repeat TPK.

The second case was a 14-year-old boy who developed Pythium infection after having a bath in pond water in the left eye. Presenting VA was 20/1200, two-third depth 5 x 5 mm stromal infiltrate with tentacles. Five days culture report was positive for Pythium. The child was managed conservatively with antibacterials and had a final visual acuity of 20/40 after one month.

The third case was an 11-year-old boy who had a presenting visual acuity of HM+, 6X5 mm feathery infiltrate, 2/3 depth in the right eye. There was no history of trauma, and the child was culture positive for Pythium. The child was managed conservatively for one month with antibacterials. He developed a leucomatous scar for which he was planned for PKP.

The fourth case was a 14-year-old girl with mud injury in the left eye, presenting visual acuity was 20/1200, 5 x 5 mm full-thickness corneal infiltrate with a history of injury since five days. She was culture positive for Pythium, for which she was managed with antibacterials for two months. She had excellent visual recovery with a VA of 20/30 on the last visit.

The fifth case was a nine-year-old boy who had a stick injury in the right eye post which he developed a 5 x 3 mm anterior stromal infiltrate with hyphated edges. He was culture positive for PK. He underwent TPK 1 month later; after three months, he was under PKP + IOL. On follow up at one year, he had a failed graft with corneal opacity with final visual acuity of HM+

The sixth case was a nine-year-old girl who had developed a 5X5 mm peripheral stromal
infiltrate with tentacular projection post stick injury in RE. She was culture positive for Pythium, managed conservatively with antibacterials and glue, and BCL for stromal melt. She underwent TPK for descemetocele. She had a leucomatous opacity two months of follow-up and was planned for PKP.

The last case was a 13-year girl who developed a 6 x 6 mm full-thickness cheesy infiltrate and landed with perforation after six days in the right eye. The presenting visual acuity was 20 / 600. She was culture positive for Pythium and underwent TPK 1 week later.

Badenoch et al. [7] reported a case of Pythium in an Australian child after swimming in a pool. The conservative management with PHMB and Voriconazole was an unsuccessful post in which he underwent TPK. We treated our patient with antibacterials as per the in vitro susceptibility evidence shown by Bagga et al. Three of our patients healed with medical management, thus proving the efficacy of antibacterials. Moreover, the majority of the previous reports list TPK as the treatment of choice for this devastating entity. Rapidly progressive infiltrate, early, or impending perforation, AC exudates and infiltrate involving limbus should undergo early TPK. Four of our patients also underwent TPK to salvage the eye. But owing to the small sample size, it is difficult to pinpoint treatment with conclusive evidence. The strengths of our study were successful management of 2 patients with good visual acuity, three healed with medical treatment, early and prompt intervention. There was no case of endophthalmitis, evisceration, or Phthisis bulbi. The limitations were small sample size, retrospective analysis, none of the patients underwent PCR, and non-availability of confocal microscopy. There are limited reports of pediatric Pythium keratitis in the available literature. A prospective study with a larger sample size would help us to arrive at better conclusions. Further large-scale randomized clinical trials are needed to exactly pinpoint more appropriate and definitive medical therapy.

CONCLUSION

Pediatric Pythium keratitis is an entity less reported to date. It closely mimics fungal
keratitis and needs early and prompt intervention in the form of antibacterial 0.2% Linezolid or 1% Azithromycin to salvage the eye and prevent vision-threatening sequelae in the form of corneal opacity, amblyopia, endophthalmitis, or Phthisis bulbi. TPK remains the mainstay of treatment in aggressive and non-resolving cases. Besides this, cyanoacrylate glue can be a potential treatment modality to salvage vision in cases with early stromal melt.

All ophthalmologists should be aware of this vision-threatening keratitis as a differential in the pediatric age group as treatment is poles apart compared to fungal keratitis.

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Next Generation Rapid Tear Diagnostic Kit For Refractive Surgery

Dr. Pooja Khamar

INTRODUCTION:

Higher levels of inflammatory factors (IL-6, IL-8, MMP-9), result in dry eye disease (DED) and may have implications for recovery of patients undergoing refractive surgery. We therefore, tested the efficiency of simple, rapid multi-analyte tear based system for measuring multiple inflammatory factors for clinical applications.

METHODS:

Tear samples were collected from 50 healthy controls, 50 patients with ocular surface conditions and 10 patients with intra-ocular conditions (glaucoma, diabetic retinopathy) with prior informed consent and institutional ethics approval. Using a variant of the multiplex ELISA assay system, we obtained specific cartridges for IL-6, IL-8 and MMP-9 measurement in a single test. The Schirmer’s strips were collected in 1.5ml tubes containing 300µl extraction buffer followed by agitation for 15 - 30 min. 50µl of the resulting extract was added to each sample well of the cartridge. 1 ml of the specific wash buffer was added to the designated buffer well. The cartridge was loaded into the analyser.
instrument which took 90 minutes to deliver the measured values on the basis of established internal references for each analyte.

RESULTS:

All three analytes (IL-6, IL-8 and MMP-9) were significantly (P < 0.05) higher in ocular surface conditions. The instrument generated RFU (relative fluorescence units) values from each sample were normalised to the wetting length. IL6 and MMP9 were log-fold higher in dry eye disease (DED) and Steven-Johnson syndrome (SJS) samples (P < 0.05) while ocular surface chemical injury samples only had high levels of IL8 (P < 0.05). IL8 levels were slightly elevated in case of the non-ocular surface conditions glaucoma and diabetic retinopathy, which has several fold lesser than that observed for DED and SJS. The data demonstrated detection of all three analytes in the 50µl sample that allowed for sufficient sample remaining if reruns are required.

CONCLUSION:

The data demonstrates that IL6, MMP9 and IL8 levels were detectable across the entire set of patient samples and show clear disease based separation of values. The efficiency and short test duration can significantly assist screening protocols in dry eye and refractive surgery to enable better patient stratification.
Botulinum Toxin Augmented Strabismus Surgery In Large Angle Esotropia- Saviour In Disguise

Dr. Sayali Mahajan

PURPOSE:
To determine effect of botulinum toxin (BT) augmentation on bimedial recession surgery in children with large-angle esotropia (ET) > 50 prism diopters (PD)

DESIGN:
Prospective interventional case series in a tertiary centre in south India. Fourteen children with large angle ET > 50 PD underwent bimedial recessions augmented with 2.5 units of BT to each MR muscle intraoperatively and were followed up for 2 years. Surgery was considered successful if patients had < 10 PD of deviation and did not require additional surgery.

RESULTS:
The mean preop deviation was 65 PD (range 50 – 80 PD). Successful outcome was seen in 10 of 14 patients (71.42 %), p < 0.001. Of these 10, 7 had sensory fusion on worth 4 dot test. Of the rest 4, 3 had residual small angle ET and 1 developed consecutive exotropia
CONCLUSION:

For children with large angle ET (>50 PD), two muscle surgery may not be adequate. BT augmentation is a safer alternative, preserving third muscle for future need and helps to achieve satisfactory binocular alignment.

INTRODUCTION

Infantile esotropia is defined as an esodeviation of unknown etiology that manifests before the age of 6 months. It is the most common type of strabismus in infancy, with an estimated prevalence of 0.3 - 0.5%. It is seen that the deviation is not present at birth but develops around the age of 2 - 4 months. When the angle reaches above 40 PD it is unlikely to resolve by itself. The purpose of this study is to report long-term outcomes for children with large-angle infantile esotropia.

MATERIALS AND METHODS

The study design was a non-randomized clinical study and was conducted at a tertiary-care pediatric hospital. Institutional Review Board (IRB) approval was obtained prospectively. The study conformed to research adhered to the tenets of the Declaration of Helsinki.

The study was conducted for all patients less than 7 years of age with esotropia of at least 50 PD. Patients were excluded who had undergone previous ocular surgery, who had major neurologic abnormalities, or who were unavailable for follow-up for a minimum period of six weeks following surgery.

Deviation was measured by prism cover test on accommodative target at distance (6 m) and near (33 cm); measurements within 5 PD on two consecutive visits were required preoperatively. Measurements for children too young for accurate prism cover test measurements at distance were obtained at near only. Versions were recorded. For cycloplegic refractions, instillation of one drop (20 μL) of 1.0% cyclopentolate hydrochloride was followed by a second drop five minutes later; retinoscopy was
performed after a 40-minute interval. Refractions were repeated on subsequent visits until retinoscopic findings agreed within 0.5 diopter (D). Two patients had a cycloplegic refraction of +2.00 D spherical equivalent or greater and these were placed in their full cycloplegic correction before surgery. Any patient who had amblyopia was treated by full-time occlusion therapy until the visual acuities of the two eyes were less than one line’s difference, or until the fixation pattern was equal. The sensory status was assessed by fusion to Worth’s four-dot test and by the Titmus stereoacuity test. A total of 14 children met the criteria for the study. They underwent bimedial recessions of 5 - 6.5 mm augmented with 2.5 units of BT to each MR muscle intraoperatively.

RESULTS

The follow-up period ranged from six weeks to 2 years. Prism cover test measurements were performed under the same conditions as preoperatively. A good surgical result was defined as orthophoria +/- 10 PD both at distance and near. An esotropia greater than 10 PD was considered an undercorrection, and exotropia greater than 10 PD an overcorrection.

The mean preop deviation was 65 PD (range 50 – 80 PD). Successful outcome was seen in 10 of 14 patients (71.42%), p < 0.001. Out of these 10 patients, 7 had sensory fusion on Worth 4 dot test. Three patients had residual small angle ET and one developed consecutive exotropia.

Transient complications were common, including 2 cases (14.2 %) of transient overcorrection and 1 case (7.14 %) of transient ptosis which resolved after 4 weeks. No patients developed a transient vertical deviation. There were no long term complications from botulinum toxin injection.

DISCUSSION

The treatment of infantile esotropia consists of a uniform approach or a selective one. Uniform surgery consists of either bimedial recessions or a monocular recession-resection. The selective surgery consists of operating three or four horizontal muscles, tailoring the amount of surgery to the amount of preoperative deviation by performing
graded amounts of resection of one or both lateral rectus muscles in addition to bimedial recessions. While studies on three-muscle surgery have reported good early success rates, Many of them studies have also reported high rates of sequential exotropia of up to 24%.

Another treatment approach designed to avoid undercorrection is to perform “supra-maximal” medial rectus muscle recessions, but this is encountered with late overcorrection. Kushner studied that if the medial rectus muscle is recessed beyond a certain point, there is a significant risk of progressive late overcorrection.

The injection of botulinum toxin into the medial rectus muscles causes transient paralysis by blocking transmission at the neuromuscular junction. The direct effects of botulinum toxin may be temporary but there can be a long-lasting effect on ocular alignment. One advantage of using botulinum toxin is that a standard dose can be used for a range of deviations, which is useful because it is difficult to obtain precise measurements in young infants. A case series of 60 patients reported a high success rate (close to 90%) with botulinum toxin injections, especially in children < 7 months old. However, a large comparative study found that botulinum toxin was much less effective than surgery when the angle of deviation was greater than 35 PD, suggesting that botulinum toxin alone is likely a poor choice for patients with large angle esotropia.

Early surgery may help to promote the development of binocularity and stereoacuity. However, a study by the Pediatric Eye Disease Investigator Group found that the angle of deviation is more variable at a young age.

This study has weaknesses. The treatment strategies were not standardized. The mean follow-up was 2 years, further changes in alignment may continue to occur years and decades after surgery. Longer term data is needed to determine if and how post-operative binocularity and stereoacuity are affected by the timing of surgery.

Future studies comparing different treatment strategies would be useful since most studies to date have reported outcomes using a uniform treatment approach. Longer-term studies
would also be helpful to inform treatment decisions and provide more accurate prognostic information for children with large-angle, infantile esotropia.

REFERENCES


Chorioretinectomy For Deep Impact Ocular Trauma In Indian Eyes

Dr. Sangeet Mittal

INTRODUCTION:

Chorio-retinectomy is a relatively new procedure for deep impact ocular trauma resulting in vitreous incarceration or penetration of choroid. In 1987, Dr Zivojnovic described a surgical technique of removing incarcerated retina and scar tissue within a perforation site. Kuhn et al later published a surgical procedure called a prophylactic chorio-retinectomy to treat perforating globe within 100 h of injury. It can be done either for a prophylactic or a therapeutic purpose. It prevents proliferative vitreoretinopathy (PVR), fibrous ingrowth and epiretinal membrane formation at the site of incarceration. The procedure consists of vitrectomy with or without base shaving, 100% deep diathermy burns around incarceration site, removal of incarcerated retinal tissue and the underlying choroid and 1-2 rows of laser around the chorio-retinectomy. The aim of the paper is to present different cases who were managed using the above technique.
METHODS:

This is a retrospective analysis of 11 eyes of penetrating eye injury with or without intraocular foreign body (March 2018 to March 2020) in whom vitreous was incarcerated in posterior retina. All eyes had visual acuity greater than or equal to accurate projection of rays. The period between primary repair and vitrectomy was noted for all cases. All eyes underwent 25 / 27 gauge Pars Plana Vitrectomy (PPV) using a non-contact widefield viewing system. After completing vitreous base shaving and peripheral retinal examination for retinal tears, chorio-retinectomy was performed. A chorio-retinectomy in this study was defined as the removal of incarcerated retinal tissue with underlying choroid to the level of bare sclera 360° around the impact or perforating site of a foreign body using the 25 / 27-gauge vitreous cutter. Before chorio-retinectomy, deep endodiathermy was applied to the surrounding retina pigment epithelium and choroid that is going to be cut. This technique removed any remaining RPE exposed to the vitreous cavity. Intraocular bleeding was controlled by using endodiathermy and / or transiently raising the infusion bottle. 1-2 rows of laser was done around the chorio-retinectomy site. Perfluoropropane gas or silicon oil tamponade was done as needed.

RESULTS:

All patients included in the study were males. The average age was 28.3 ± 12.06 years. In 7 out of 11 eyes, the foreign body was intraocular and impacted in the posterior wall of globe. In 2 eyes, there was an exit wound through which the foreign body had pierced causing a double perforation. In 1 eye, the trauma was due to a knife injury and in 1 eye it was due to cow’s horn. 4 eyes had associated retinal detachment whereas 1 eye had associated endophthalmitis. Silicon oil tamponade was done in 5/11 (45.5 %) eyes. Visual improvement after surgery was seen in 10/11 (90.9 %) eyes. Recurrent PVR occurred in 2/11 (18.2 %) eyes. Retina was attached in all eyes at last follow up.
DISCUSSION:

Many studies have been published for the ideal treatment of perforating/penetrating posterior segment injuries with or without a retained IOFB. In the non-chorio-retinectomy technique, the PVR rate is between 62-89%. Pathologic findings have disclosed that PVR is the result of RPE proliferation and fibrous proliferation from the wound. During chorio-retinectomy eliminates all the exposed RPE following a foreign body injury, as well as the fibrous proliferation around the perforation/impact site. The theoretic advantage of this technique is to remove any hemorrhage and inflammatory components with PPV, and to prevent fibrous adhesions from the retina to the impact or perforation site. Additional benefits of chorio-retinectomy include removal of incarcerated vitreous and or retina into the perforation site, the removal of retained foreign body fragments in the choroid or sclera, and removal of fibroproliferative tissue at the choroid/sclera interface. The PVR rates in perforating eye injuries decreased after chorio-retinectomy techniques.

Our PVR rates were lower (18.2% vs 62%) when compared with earlier studies. All these differences may be explained by the nature of the injury; almost all of our cases were caused by intra-ocular foreign bodies, whereas most of the patients in earlier studies were wounded by conventional and unconventional fragmentary munitions.

The timing for this surgery is also controversial. Kuhn et al suggest surgery within 100 h of the injury; however, the surgery in this period is technically very difficult with lots of hemorrhage during surgery and leakage from the impact and exit wounds. We feel that early chorio-retinectomy within a week (5–7 days) can still prevent PVR related to exit / IOFB impact site and also allows removal of intravitreal blood and disconnection of the intravitreal wound tract with less leakage, hemorrhage, and corneal problems. On the other hand, some of the authors still suggest late surgery, which is 2 weeks after the injury, which gives the advantage of performing the surgery in a quite eye mostly with posterior hyaloidal detachment and without any new haemorrhage and leakage. The
cornea also becomes clearer within that period. However, PVR is the main problem in those eyes and retinal detachment is very frequent at that period. The mean period between primary repair and vitreoretinal surgery was 2 weeks in our cases, the earliest being within 2 days and latest being 40 days. We advocate performing surgery at the end of first week, which averages the advantages and disadvantages of early vs late surgery.

In our study group, final BCVA ranged from 20/20 to CF from 50 cm. Kuhn et al. in 2006 reported that 64% of all perforating trauma and 25% of IOFB injuries had a BCVA worse than 20/200. On the other hand, in these severe globe injuries, it is obvious that even the chorio-retinectomy surgical technique may fail, and eventually lead to phthisis.

Anatomical success of this extensive chorio-retinectomy technique in our study group seems to be better - (100 % globe survival and 84.6 % final reattachment rate). It is obvious that visual acuity stabilization after posterior segment ocular trauma may take many years. But we believe that there are other reasons for these comparatively lower final BCVA results. The main reason for the lower visual results is that 10 of 13 patients (77 %) had macular injury. Performing chorio-retinectomy in cases with macular injury is a controversial issue. However, we believe that chorio-retinectomy should be performed even in cases with macular impact site to augment retinal attachment and globe survival.

Another problem limiting the final vision is the presence of corneal scarring. Of 13 patients, 9 (69.2 %) had entry site involving cornea resulting in a corneal scar in our series, but none of these patients had penetrating keratoplasty yet limiting the final BCVA.

CONCLUSION:

Chorio-retinectomy in perforating eye injuries seems to prevent exit site wound-related PVR in most of the cases when performed as early as possible.
REFERENCES:


Comparative Outcomes In Endophthalmitis Caused By Biofilm Positive And Biofilm Negative Bacteria

Dr. Vivek Dave

ABSTRACT

PURPOSE

To compare the clinico-microbiological features and outcomes in patients with infectious endophthalmitis caused by biofilm-positive (BP) and biofilm-negative (BN) bacteria.

METHODS

This was a prospective, interventional, comparative, non-randomized, consecutive case series. Culture-positive bacterial endophthalmitis cases from 1st August 2018 to 31st July 2019 were included. All vitreous samples were tested for biofilm using crystal violet plate and XTT (2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide) methods and classified as BN and BP. Antibiotic susceptibility of all organisms was determined. Anatomic and functional success was defined as intraocular pressure > 5 mm Hg and a final best-corrected vision ≥ 20/400 respectively at last visit.
RESULTS

There were 50 eyes in the BN group and 33 eyes in the BP group. BN group eyes required 2.86 ± 1.45 surgical interventions, and BP group eyes needed surgical 6.36 ± 2.89 interventions, p < 0.0001, 95 % Confidence Interval, Cl. 2-4. Median follow-up was 6 and 5 months, respectively (p = 0.33). Final log MAR vision was a median of 1.2 and 1.9 respectively; p = 0.0005, 95 % C.I. 0.4 to 1.7. Functional success was achieved in 44 % and 21.2 % (p = 0.03, 95 % C.I. 1.86 % to 40.08 %) and anatomic success was achieved in 68% and 42.42 % respectively (p = 0.02, 95 % C.I. 3.85 % to 45.47 %). The antimicrobial resistance patterns between the two groups were comparable.

CONCLUSION:

Endophthalmitis caused by the biofilm-forming bacteria need a greater number of surgical interventions. The anatomic and functional outcomes are poorer than non-biofilm forming bacterial endophthalmitis. The increased virulence and poorer outcomes can be hypothesized to be due to the physical barrier effect of the biofilm to the antibiotics.

KEYWORDS:

Biofilm, bacterial endophthalmitis, clinical outcome, endophthalmitis,

INTRODUCTION

Endophthalmitis is defined as inflammation of the inner coats of the eyeball, primarily involving the vitreous. It is one of the most dreaded eye conditions. Most cases occur either following surgery or trauma. The organisms gain entry either from exogenous sources like trauma or surgery or from endogenous hematogenous spread from a distant site. [1] Bacterial endophthalmitis is more common than fungal endophthalmitis. Staphylococcus epidermidis is the most common isolate in the USA[1], Europe[2], and
Biofilm is one of the major causes of resistance to various antibiotics in systemic diseases. Structurally, a biofilm is a slimy layer of an extracellular matrix made of polymeric substances produced by microorganisms (Fig 1).

This forms an architectural colony providing resistance not only against antibiotics but also against the human immune system. Role of biofilm has been studied in several ocular conditions where implants are used (such as intraocular lens, scleral buckles, punctal plugs, and lacrimal intubation devices) and not used (such as keratitis, chronic dacryocystitis, and endophthalmitis). Microorganisms produce biofilm by various mechanisms related to biochemical, molecular, and altered host factors. Leid et al demonstrated the development of histologically proven biofilm on the posterior surface of the lens capsule about 72 h after injecting 5000 cfu/ml of S. aureus RN 6390 into the mid-vitreous cavity in a murine model.
There are no reports on the impact of biofilm on the clinical management of endophthalmitis and its outcome in existing literature. In the current communication, we present our results of evaluating bacterial biofilm and its role in the management outcome of endophthalmitis.

METHODS

This was a prospective, comparative, non-randomized, consecutive case series. Patients diagnosed with culture-positive bacterial endophthalmitis from 1st August 2018 to 1st August 2019 were recruited into the study. Data of patients with a minimum follow-up of 3 months were analyzed. The study was approved by the Institutional Review Board (LEC-7-18-118) and adhered to all the tenets of the Declaration of Helsinki on treating human subjects. Written informed consent was obtained from all patients and guardians, when patients were younger than 18 years. The exclusion criteria included all culture-negative cases of infectious endophthalmitis, all cultures positive for fungus, and patients not consenting to the study.

All patients underwent a detailed, comprehensive ophthalmic evaluation including uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA) using Log MAR chart, slit-lamp biomicroscopy, intraocular pressure (IOP) by Goldman applanation tonometry (GAT), a dilated fundus examination using 78/90/20 D lens, and B-Scan ultrasound evaluation when fundus was not visible. Endophthalmitis was diagnosed clinically (and with B-scan ultrasonography, when required) from a combination of symptoms (pain, red eye, lid edema, reduced presenting vision) and signs (corneal edema, exudates in the anterior chamber, hypopyon, vitreous exudates, medium to high reflective dot or membranous opacities in the vitreous cavity and a thickened choroid).

Undiluted vitreous was processed in microbiology laboratory for direct microscopy and culture for bacteria and fungi as per the institutional protocol. [9] The bacterial isolates
were identified by Vitek 2 compact system (bioMerieux), and antibiotic susceptibility was tested by a combination of E test and Vitek 2 for minimum inhibitory concentration (MIC) of several antibiotics and interpreted as per CLSI (Clinical and Laboratory Standards Institute) guidelines. The bacterial isolate was then tested for biofilm formation in vitro using crystal violet method and XTT (2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide) method. (Fig 2).

Functional success was defined as visual acuity logMAR 1.3 (Snellen >20/400) and anatomical success as IOP >8 mm Hg. [3]

**CLINICAL MANAGEMENT PROTOCOL**

As per institute protocol, the surgical management of endophthalmitis consisted of pars plana vitrectomy, microscopy and culture of undiluted vitreous, antimicrobial susceptibility testing of bacterial isolates, intravitreal antibiotics (vancomycin (1 mg /
0.01 ml) + ceftazidime (2.25 mg / 0.01 ml) with or without dexamethasone (400 μg / 0.01 ml). The medical treatment also included intensive topical antibiotics (ciprofloxacin 0.3% one hourly) and corticosteroid (prednisolone acetate 1% one hourly) and oral ciprofloxacin 750 mg two times per day for 7-10 days. Additional procedures such as repeat intravitreal antibiotics or repeat pars plana vitreous lavage depended on the response to treatment and were left to the decision of the treating physicians. In principle, intravitreal injections were repeated every 48 hours. Media clarity was recorded in terms of reduction of vitreous echoes on B scan at each subsequent visit and in terms of improvement in the visibility of the retina and retinal vessels. Repeat injections were discontinued once media clarity increased to at least second order retinal vessels visible. In cases with hazy view due to corneal involvement, a vitreous biopsy was taken instead of a vitrectomy procedure. The topical and intravitreal antibiotics used were adjusted as per the culture sensitivity report.

STATISTICAL METHODS

The collected data was arranged on an excel spreadsheet. Statistical analysis was analyzed using the MedCalc Statistical Software version 19.7.2 (MedCalc, Ostend, Belgium). All continuous data were classified as either normative or non-normative in each group. Paired t-test was used to compare normative data, and the Mann-Whitney U test was used to compare non-normative data. Analysis of categorical data was done using the chi-square test. Odd’s ratio was calculated wherever appropriate. Multivariate logistic regression analysis was done to assess the effect of various demographic and clinical factors on the final anatomic and functional outcome. A p-value of < 0.05 was assigned as statistically significant.

RESULTS

Eighty-three patients satisfied the inclusion criteria in the study period of one year. Fifty patients’ were biofilm positive, and 33 patients were biofilm negative with either CVP or
XTT method, or both. Demographic details of the patients in both groups are given in Table 1. There was no statistical difference in the presenting age, duration of vision loss, or presenting vision between the groups. The proportion of males in the two groups were 78.8% and 56% respectively (p= 0.03). The etiology of endophthalmitis was comparable in both groups (Table 2).

<table>
<thead>
<tr>
<th>Event</th>
<th>Biofilm negative</th>
<th>Biofilm positive</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post cataract surgery</td>
<td>21 (42%)</td>
<td>13 (39.39%)</td>
<td>0.81</td>
</tr>
<tr>
<td>Post open globe injury</td>
<td>20 (40%)</td>
<td>14 (42.42%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Endogenous</td>
<td>6 (12%)</td>
<td>3 (9.09%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Post keratoplasty</td>
<td>1 (2%)</td>
<td>0</td>
<td>0.41</td>
</tr>
<tr>
<td>Post trabeculectomy</td>
<td>0</td>
<td>2 (6.06%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Post vitreoretinal surgery</td>
<td>1 (2%)</td>
<td>1 (3.03%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Post keratoprosthesis</td>
<td>1 (2%)</td>
<td>0</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Table 2. Various etiologies of endophthalmitis in the two groups
Vitreous biopsy was performed in all patients. It showed a combination of gram-positive and gram-negative organisms (Table 3). In general, biofilm production was similar, 38.1 % (n= 16 of 42) in gram-positive bacteria and 41.5 % (n= 17 of 41) in gram-negative bacteria; it was seen more often in Staphylococcus spp. (68.7 %; n = 11 of 16 biofilm producing positive bacteria) and Pseudomonas spp. (64.7 %; n = 11 of 17 biofilm producing gram-negative bacteria) (Table 2). The antibiotic resistance pattern is listed in Table 4.

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Biofilm negative</th>
<th>Biofilm positive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Streptococcus species</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S pneumoniae</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>S anginosus</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>S pyogenes</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>S mitis</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>S licheniformis</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>S gordonii</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>S agalactia</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td><strong>Staphylococcus species</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S epidermidis</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>S aureus</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>S lugdunensis</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>---------------------------</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Bacillus species</td>
<td>B cereus</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>B licheniformis</td>
<td>1</td>
</tr>
<tr>
<td>Gemella species</td>
<td>G morbillorum</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Total. n= 42</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>26 (61.9%)</td>
<td>16 (38.1%)</td>
</tr>
<tr>
<td>Gram negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas species</td>
<td>P aeruginosa</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>P stutzeri</td>
<td>3</td>
</tr>
<tr>
<td>Stenotrophomonas species</td>
<td>S maltophilia</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Aeromonas species</td>
<td>A hydrophila</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Brevundimonas species</td>
<td>B vesicularis</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Escherichia species</td>
<td>E Coli</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Acinetobacter species</td>
<td>Alwoffii</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Klebsiella species</td>
<td>K pneumoniae</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Enterobacter species</td>
<td>E aerogenes</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>E cloacae</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>S marcescens</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Cronobacter sakazakii</td>
<td>C sakazakii</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Pantoea species</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Total. n= 41</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 (58.5%)</td>
<td>17 (41.5%)</td>
</tr>
</tbody>
</table>

Table 3. Microorganisms isolated in the biofilm positive and biofilm negative groups
### Table 4

<table>
<thead>
<tr>
<th>Antibiotic tested for resistance</th>
<th>Biofilm negative group</th>
<th>Biofilm positive group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>4.52% (n=22)</td>
<td>10% (n=10)</td>
<td>0.55</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>60.86% (n=23)</td>
<td>33.33% (n=15)</td>
<td>0.1</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>31% (n=29)</td>
<td>35.29% (n=17)</td>
<td>0.76</td>
</tr>
<tr>
<td>Amikacin</td>
<td>52.63% (n=19)</td>
<td>40% (n=15)</td>
<td>0.47</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>20% (n=45)</td>
<td>34.48% (n=29)</td>
<td>0.16</td>
</tr>
<tr>
<td>Imipenem</td>
<td>66.66% (n=15)</td>
<td>30% (n=10)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

**Table 4. Comparison of antibiotic resistance patterns between the two groups**

In the negative biofilm group, 34 (68 %) eyes met the criteria of anatomical success, and 22 (44 %) eyes met the criteria of functional success. Comparatively, in the positive biofilm group, 14 (42.4 %) eyes and 7 (21.2 %) eyes met the anatomical and functional success criteria, respectively. The biofilm negative and positive group differed in both the anatomical (p = 0.02) and functional (p = 0.03) success. Further, the eyes with positive biofilm infection needed a statistically greater number of surgical interventions (p < 0.0001). Despite an increased number of surgical interventions, final visual acuity remained poor in biofilm-positive endophthalmitis patients. Logistic regression analysis
showed no influence of other demographic or clinical factors on the final anatomic or functional outcome. (Table 5).

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Anatomic outcome</th>
<th>Functional outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>95% C.I.</td>
</tr>
<tr>
<td>Age</td>
<td>1</td>
<td>0.92 to 1.09</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.63</td>
<td>0.16 to 2.4</td>
</tr>
<tr>
<td>Duration of vision loss</td>
<td>0.81</td>
<td>0.64 to 1.01</td>
</tr>
<tr>
<td>Non-cataract etiology for endophthalmitis (reference odds ratio of 1 for post-cataract surgery etiology)</td>
<td>0.4</td>
<td>0.1 to 1.6</td>
</tr>
<tr>
<td>Presenting vision in logMAR</td>
<td>2.95</td>
<td>0.28 to 30.2</td>
</tr>
</tbody>
</table>


Table 5. Multivariate logistic regression analysis for the effect of various factors on the final favorable clinical outcome

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of surgical intervention</td>
<td>0.93</td>
<td>0.85 to 1.01</td>
<td>0.12</td>
</tr>
<tr>
<td>Number of interventions</td>
<td>1.14</td>
<td>0.86 to 1.53</td>
<td>0.33</td>
</tr>
<tr>
<td>Vancomycin resistance</td>
<td>1.83</td>
<td>0.11 to 7.98</td>
<td>0.97</td>
</tr>
<tr>
<td>Ceftazidime resistance</td>
<td>0.7</td>
<td>0.09 to 6.68</td>
<td>0.82</td>
</tr>
<tr>
<td>Absence of Biofilm formation</td>
<td>3.62</td>
<td>1.77 to 6.88</td>
<td>0.02</td>
</tr>
</tbody>
</table>

DISCUSSION

The current study discusses the role of biofilm in the treatment outcome of bacteria endophthalmitis. It was noted that bacteria with in-vivo biofilm formation in endophthalmitis showed enhanced in-vivo virulence leading to an increased need for surgical intervention and reduced final anatomic and functional success. The current study also included cases that were post-trauma. Trauma by itself is a confounding factor that can directly affect final clinical outcomes irrespective of the severity of endophthalmitis. However, as the number of cases post-trauma in both groups was comparable (p = 0.82), the effect of this confounding variable was avoided. Griffiths et al. reported biofilm formation on an IOL by S. epidermidis in 1989. 13 Adherence of the bacteria to the lens with glyocalyx around it prevents both antibiotics and antibodies from reaching the bacteria. Increased adherence of S. epidermidis to intraocular
polypropylene lenses compared to polymethylmethacrylate lenses are known.\textsuperscript{14} It is proposed that biofilm production on IOLs after cataract surgery occurs due to the microorganism’s ability to adhere to these lenses via exo-polysaccharides produced by them. This provides an extra shell and protects these bacteria from the antibiotics.\textsuperscript{15,16} Need for multiple interventions and eventually the IOL explantation has also been reported in acute and chronic biofilm-producing Staphylococcal endophthalmitis.\textsuperscript{17} However, biofilm formation is not always associated with antibiotic resistance but may affect virulence. Biofilm producing S. epidermidis produces extracellular polymeric substances and inhibits phagocytosis and antibiotics’ action, resulting in inadequate clearance of organisms.\textsuperscript{18} Hence in these situations, multiple interventions may be required to sterilize the vitreous cavity. The current study showed the need for significantly more interventions in biofilm-producing microorganisms causing endophthalmitis as compared to those that were biofilm-negative.

Biofilms have been known to have a virulent role in ophthalmology, especially in cases where some kind of implant has been used for management of the disease. A study conducted by Holand et al, has demonstrated biofilm in 65\% of scleral buckles (solid silicone and sponge forms) removed for infection and extrusion by scanning electron microscopy.\textsuperscript{19} Biofilms on scleral buckles may function as reservoirs for pathogenic bacteria contributing to its extrusion.\textsuperscript{20} A report by Yokoi N et al, has shown association of biofilm in punctal plugs developing conjunctivitis that required removal of the plug and prolonged antibiotic treatment.\textsuperscript{21} Periorbital implants include orbital plates, porous polyethylene floor implant, orbital sphere implants, anophthalmic socket sphere implants or metal screws. Scanning electron microscopy has demonstrated polymicrobial or mixed species biofilm on these implants. However, most commonly seen organism in orbital implants was S. aureus. Other organisms included M. chelonae, Pantoea agglomerans found in polymicrobial cases, yeasts (Candida spp., and Trichosporonspp.), Staphylococcus spp., M. chelonae and Gram-negative bacilli.
(Achromobacter xylosoxidans and P. aeruginosa) in orbital plates. Virulence related to biofilm formation has also been proposed in contact lens-related keratitis. One of the commonest organisms implicated in contact lens associated keratitis is Pseudomonas species which is also known to form biofilm. A study conducted by Abidi et al, has shown that all species of Pseudomonas were found to be potential biofilm formers and also concluded that the multi-drug resistant isolates displayed significant biofilm production as compared to susceptible isolates indicating the anti-microbial resistance offered by the biofilm to these organisms. Biofilm also forms with Acanthamoeba spp. which is another most common organism involved in contact lens associated keratitis.

The current study had its strengths and limitations. Among strengths, this was a prospective consecutive case series where the patients were treated by a uniform institutional protocol, but the treating physicians were masked to the results of the biofilm. Among limitations, the biofilm formation was tested in-vitro in cultures and not over IOLs because its explantation was not needed in any of the patients. Thus, our study is an in-vivo extrapolation of the in-vitro observation. Furthermore, the cases in this study also included etiologies other than intraocular surgery, such as open globe injury. This makes the instances heterogeneous, but a logistic regression analysis did not impact the etiological differences on the final clinical outcome.

CONCLUSION

We propose that early identification of biofilm-forming organisms may help decide a tailored management strategy for each patient. It would also help in proper prognosticating the outcome. These results can serve as a background for further research into anti-biofilm measures impacting clinical outcomes in patients with endophthalmitis.
REFERENCES


FIGURE LEGENDS

1. Cartoon showing the pathophysiologic cycle of formation of biofilms. The organisms attach on the tissue surface followed by colonization. Colonization is followed by laying down of lipids, nucleic acids, polysaccharides and proteins which form the structure of the biofilm

2. Photograph showing negative and positive controls for biofilm formation by the crystal violet method (Top Panel) and the XXT method (Bottom panel)

TABLE

<table>
<thead>
<tr>
<th></th>
<th>Biofilm negative</th>
<th>Biofilm positive</th>
<th>P-value</th>
<th>95% C.I. for the difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of eyes</td>
<td>50</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males (%)</td>
<td>28 (56)</td>
<td>26 (78.8)</td>
<td>0.03</td>
<td>1.86% to 40.08%</td>
</tr>
<tr>
<td>Mean age in years (median)</td>
<td>44.08 ± 24.67 (50.5)</td>
<td>46.51 ± 19.24 (49)</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>Duration of vision loss in days (median)</td>
<td>4.48 ± 5.63 (2.5)</td>
<td>4.83 ± 7.44 (2)</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Post cataract surgery (%)</td>
<td>21 (42)</td>
<td>13 (39.4)</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Presenting vision in logMAR (median)</td>
<td>2.79 ± 0.72 (3.3)</td>
<td>2.72 ± 1.13 (3.3)</td>
<td>0.69</td>
<td></td>
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<tr>
<td>-------------------------------------</td>
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<td></td>
</tr>
<tr>
<td>Glaucoma at presentation</td>
<td>16 (32%)</td>
<td>10 (30.3%)</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>Vitreous tap as first procedure</td>
<td>12 (24.5%)</td>
<td>7 (22.6%)</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Gram negative etiology</td>
<td>24 (48%)</td>
<td>17 (51.51%)</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>Mean number of surgical interventions (median)</td>
<td>2.86 ± 1.45 (3)</td>
<td>6.36 ± 2.89 (6)</td>
<td>&lt;0.0001</td>
<td>2 to 4</td>
</tr>
<tr>
<td>Follow up in months (median)</td>
<td>6.96 ± 5.16 (6)</td>
<td>5.8 ± 4.74 (5)</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>Final vision in logMAR (median)</td>
<td>1.2 ± 0.57 (1.2)</td>
<td>2.17 ± 0.88 (1.9)</td>
<td>0.0005</td>
<td>0.4 to 1.7</td>
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<tr>
<td>Functional success</td>
<td>22 (44%)</td>
<td>7 (21.2%)</td>
<td>0.03</td>
<td>1.86% to 40.08%</td>
</tr>
<tr>
<td>Anatomic success</td>
<td>34 (68%)</td>
<td>14 (42.42%)</td>
<td>0.02</td>
<td>3.85% to 44.47%</td>
</tr>
</tbody>
</table>

Table 1. Comparative presentations and outcomes of biofilm negative and biofilm positive organisms
Dr. Vivek Dave  MD, DNB, FRCS(UK), FICO(UK), MNAMS
Consultant Vitreo Retina
Smt. Kanuri Santhamma Centre for
Vitreo Retinal diseases
LV Prasad Eye Institute
Hyderabad

Sub-Retinal Injection Of Stem Cell-Derived Rpe Cells: 6 Month Safety And Integration In A Rat Model
Dr. Vivek Dave

The study was carried out in Royal College of Surgeon (RCS) rats that undergo gradual retinal degeneration over a period of 6-8 months. Human induced pluripotent stem cell-derived RPE cells prepared under standardized GMP controlled conditions were injected into the sub-retinal space of one eye of 4 weeks old RCS rats (N=10). About 0.5-1×105 cells in 3-5 µL were injected using a 28G needle & Hamilton syringe. Prior to injection and post injection, the rats were maintained under immunosuppression by oral cyclosporine administration in the drinking water. At 6-month follow up, fundus examination revealed visible patches of pigmented RPE cells, which were well positioned within the sub-retinal space. They neither showed abnormal proliferation nor formed any visible tumors. Immunostaining using anti-PAX6 and anti-Human mitochondrial antibodies confirmed that the pigmented cells are of human origin. None of the animals showed any signs of local or systemic inflammation or adverse events.
ABSTRACT:

PURPOSE:

To evaluate the surgical outcomes of a modified approach in the management of submacular hemorrhage secondary to polypoidal choroidal vasculopathy (PCV) using microscope integrated intraoperative optical coherence tomography (miOCT).

STUDY DESIGN:

Retrospective case-series

METHODS:

10 eyes of 10 patients underwent 23-gauge vitrectomy, followed by miOCT guided submacular injection of recombinant tissue plasminogen activator (12.5 μg/0.1 mL), Bevacizumab (2.5 mg/0.1 mL), and air (0.3 mL). Written informed consent was obtained in each case. Propped-up positioning was advised in postoperative period. Patients were evaluated for changes in best corrected visual acuity (BCVA), time taken for the...
displacement of submacular bleed, recurrence of bleed and occurrence of any intraoperative or postoperative complications. All cases were followed up for 6 months after the initial surgery.

RESULTS:

Complete displacement of hemorrhage from macula and resolution of bleed was achieved in all cases. The average time taken was 7.6 ± 6.6 weeks (2-24 weeks). Mean BCVA at baseline was 1.64 ± 0.4 logMAR units (1-2.1 logMAR units), which showed significant improvement to 1.13 ± 0.46 logMAR units (0.5-1.8 logMAR units) at 1 month (p = 0.0061) and 0.82 ± 0.46 logMAR units (0.5-1.7 logMAR units) at 6 month follow-up visit (p = 0.0005).

CONCLUSION:

Favorable outcomes were achieved due to effective displacement of hemorrhage and simultaneous treatment of the underlying pathology. miOCT guidance aids in precise delivery of the drug into the subretinal space.

INTRODUCTION

Submacular hemorrhage refers to the accumulation of blood between the retinal pigment epithelium and neurosensory retina and/or under the RPE. It occurs mostly secondary to various conditions like neovascular age-related macular degeneration (AMD), polypoidal choroidal vasculopathy (PCV), myopia, trauma, presumed ocular histoplasmosis syndrome, angioid streaks, etc.1-3 The prognosis can be poor in cases of old, thick submacular hemorrhage which may extend beyond vascular arcades.4

PCV is a variant of neovascular AMD. Recurrent submacular hemorrhages are common in PCV. As compared to AMD, PCV has a more stable and favorable course if managed appropriately.5
Various techniques have been described in the literature for the management of vision-threatening submacular hemorrhage but the surgical management of submacular hemorrhage in cases of PCV needs to be extensively studied. With the advent of miOCT, real time imaging is available intraoperatively, resulting in better clinical judgments.

In this study, we have tried to find out the efficacy of pneumatic displacement of subretinal blood by adopting a modified technique of pars plana vitrectomy followed by miOCT guided subretinal injection of recombinant tissue plasminogen activator (r-tPA) (12.5 μg/0.1 mL) and Bevacizumab (2.5 mg/0.1 mL), along with 0.3 mL of air. Favorable outcomes have been previously reported by us in cases of submacular hemorrhage secondary to neovascular AMD, using the above technique.

MATERIALS AND METHODS:

A retrospective chart review of patients presenting with submacular hemorrhage attributable to PCV was done. All those cases which underwent 23 gauge (G) pars plana vitrectomy followed by miOCT guided subretinal injection of r-tPA, Bevacizumab and air, were included in the study. Selection bias was avoided by recruiting all consecutive patients. Written informed consent was obtained from all patients. The study adhered to the tenets of the Declaration of Helsinki.

10 eyes of 10 patients suffering from submacular hemorrhage secondary to PCV were included in the study. The baseline evaluation included acquisition of demographic details, best corrected visual acuity (BCVA), history of presenting symptoms, details of previous treatment and history related to systemic illness. All cases underwent a thorough ocular and systemic examination. Ocular examination involved detailed anterior and posterior segment evaluation. The maximum area of hemorrhage was noted in disc diameter (DD). All the cases were subjected to investigations like fundus photography, swept source optical coherence tomography (SS-OCT) and Indocyanine green angiography (ICGA). Due
to its longer wavelength, ICGA had the advantage of deeper penetration of rays in areas of hemorrhage, resulting in better imaging. A clinical diagnosis of PCV was made in all those cases in which SS-OCT showed presence of thumb like pigment epithelial detachments (PED), double layer sign or tomographic notch sign. The cases in which ICGA showed presence of polyps with a halo of hypofluorescence around the nodule were also included. (Figure 1) Postoperatively, the diagnosis of PCV was confirmed with the help of SS-OCT and ICGA.

Before starting the surgery, a solution of r-tPA (Boehringer Ingelheim Pharma GmbH & Co, KG, Germany) having a concentration of 1 mg/mL was made by dissolving 20 mg r-tPA in 20 mL of sterile water. Further dilutions were done to achieve a final concentration of 12.5 μg/0.1 mL. 0.3 mL of sterile air was loaded in a 1 mL sterile tuberculin syringe. 0.1 mL Bevacizumab (2.5 mg) {Avastin; Genentech, South San Francisco, California} was then loaded in the syringe. Finally, 0.1 mL of reconstituted r-tPA (12.5 μg/0.1 mL) was drawn. Thus, the total volume of cocktail was 0.5 mL.

Under sterile setting and regional anaesthesia, a standard 3 port 23 G pars plana vitrectomy was performed. Posterior vitreous detachment was induced in all cases. miOCT was used to confirm the site of involvement and to look for any pigment epithelial detachment (PED). The final site of injection was determined using miOCT to avoid any inadvertent injection into PED. The cocktail was then injected subretinally after creating a self-sealing retinotomy using 41 G needle attached to tuberculin syringe. Thus, a small localized bullous retinal detachment was created extending a little beyond the hemorrhage. Air fluid exchange was performed followed by injection of 20% SF6 gas to provide short term tamponade. Propped up position was advised for 3-5 days in the postoperative period.

All cases were followed-up regularly until 6 months after the surgery. Details regarding BCVA, displacement of hemorrhage and any postoperative complication was recorded at
each follow-up visit. Detailed anterior, posterior segment examination, color fundus photography and SS-OCT were done at each visit. Cases were subjected to ICGA on a pro re nata basis. In this study, the findings at postoperative 1 month and 6-month visits were analyzed.

Statistical analysis was done using SPSS version 21 software. The continuous data were evaluated using paired t-test. The categorical data were analyzed using Pearson chi square test and Fisher’s exact test. A p-value d”0.05 was deemed statistically significant.

RESULTS:

Out of 10 patients, 6 patients were male and 4 were female. The mean age of the patients was 67.5 ± 12 years (range, 51-83 years). The average duration of symptoms was 8.8 ± 5.7 days (range, 2-21 days). The centre of fovea was involved by submacular hemorrhage in all cases on SS-OCT. 4 cases (40%) had hemorrhage extending to vascular arcades.

Mean preoperative BCVA was 1.64 ± 0.4 logMAR units (range, 1-2.1 logMAR units). Displacement of bleed was noticed in all eyes on the first postoperative day. Complete displacement of hemorrhage from macula and resolution of bleed was achieved in all cases. Figure 2, 3 represent successful outcome in the operated cases. The average time taken was 7.6 ± 6.6 weeks (range, 2-24 weeks). Mean postoperative BCVAs of 1.13 ± 0.46 logMAR units (range, 0.5 - 1.8 logMAR units) and 0.82 ± 0.46 logMAR units (range, 0.5-1.7 logMAR units) were achieved at 1 month and 6 month visits, respectively. There was a statistically significant improvement in visual acuity from preoperative BCVA of 1.64 ± 0.4 logMAR units to 1.13 ± 0.46 logMAR units at 1-month follow-up (p = 0.0061). Similarly, visual acuity continued to improve up to 0.82 ± 0.46 logMAR units at 6 months follow-up visit (p = 0.0005). No intraoperative or postoperative complication was noted after the surgery. Only one case had a rebleed which was managed conservatively with repeat Intravitreal anti-VEGF injection leading to improvement in vision with final BCVA of 0.8 logMAR units at 6-month follow-up.
DISCUSSION:

PCV is characterized by the presence of slow-growing, complex neovascularization that has a branching vascular network (BVN) with aneurysmal dilations at the outer border of the network. It is highly prevalent in Asian races. One of the usual presentations of PCV is recurrent submacular hemorrhage which can have variable prognosis depending upon volume (horizontal extent and thickness) and duration of the hemorrhage.

Various techniques have been described in the literature which focus on the pneumatic displacement of bleed with intra-vitreal gas alone or in combination with adjuncts like intravitreal r-tPA or anti-VEGF agent. Lin et al. studied 20 cases with PCV and submacular hemorrhage who received either intravitreal injection of tPA and gas or subretinal tissue plasminogen activator (tPA) with vitrectomy. Better results were obtained in the vitrectomy arm.

Haupert et al. first described the technique of subretinal tPA along with pneumatic displacement in cases of subretinal bleed due to neovascular AMD. Main drawback was sequential management of the underlying pathology rather than simultaneous management, which is pertinent. Hence, modifications were made and published by Martel and Mahmoud et al. in cases of choroidal neovascular membrane (CNVM), where they performed 23 G vitrectomy along with injection of subretinal tPA (12.5 µg/0.1mL) with bevacizumab and air. Prone positioning was advised. They treated the CNVM simultaneously by halting its progression.

The above studies encouraged us to modify the technique. Using a 23 G translocation needle, a bullous neurosensory detachment was created by directly injecting a cocktail of subretinal tPA, Bevacizumab and air and intravitreal 20% SF6. Direct injection of tPA helped in liquefaction of clot as studies have shown that displacement of clotted blood without prior dissolution causes damage to photoreceptor cells. To prevent rebleed, injection bevacizumab was also injected subretinally in the dose of 2.5mg/0.1mL. Treumer
et al. showed the efficacy of vitrectomy with subretinal application of tPA and bevacizumab in cases of subretinal bleed due to CNVM.15 Although the intravitreal injection of Bevacizumab does produce an effect but the direct injection into the subretinal space ensures direct drug delivery over the pathological lesion. Thus, direct high dose injection was used in our study. Subretinal air (0.3mL) along with intravitreal gas (20% SF6) injection helped in pneumatic displacement by acting subretinally and from the vitreous side. Absorption of even sub RPE bleed is rapid due to pressure effect. Propped-up positioning helps in faster inferior displacement of bleed as compared to prone position. Identification of appropriate site for needle penetration can be challenging, miOCT guidance can help in visualisation of retinal microarchitecture and proper localisation of needle/cannula. PIONEER study has shown positive results in this aspect.10

In the present study, complete displacement of bleed was achieved in all cases with no major intraoperative or postoperative complications. Early presentation within 1-2 weeks of the onset of symptoms helped in achieving favorable visual outcomes. Rebleeds and breakthrough hemorrhages are common in PCV. One patient developed rebleed and was managed successfully with intravitreal injection of anti-VEGF agent (Aflibercept) as it reduced the permeability of abnormal choroidal vessels and polyps.8 Thus, all the patients experienced significant visual improvement due to timely intervention and effective clot displacement. The use of 41G translocation needle reduces the chance of rhegmatogenous retinal detachment and miOCT guidance further helps in precise delivery of drugs, making it a safe procedure. Similar results were obtained by us in cases of neovascular AMD, reiterating the efficacy of the above technique.11

The study has its limitations due to the limited sample size and the retrospective nature of the study. Further prospective studies like randomized control clinical trials (RCT) can help in establishing the efficacy and safety of this technique.
REFERENCES:


Can Rate Of Vascular Outgrowth Be A Predictor For Treatment In Babies With ROP?

Dr. Tapas Ranjan Padhi

ABSTRACT

PURPOSE:

To analyze the retinal vascular growth rate in treatment naïve babies with various stages of Retinopathy of Prematurity (ROP) and validate if this could be a predictor of treatment need.

METHOD:

Retrospective review of medical charts and retinal images of babies with various stages of ROP. Using the length of the horizontal disc diameter (DD) of each eye, the vessel growth was measured from the disc margin up to the vessel tip in fixed quadrants. The rate of vessel growth was the ratio of vessel length to the number of weeks it took to reach this length. The babies studied were divided into treatment warranting ROP (Group 1), spontaneously regressed (Group 2), and no-ROP (Group 3) for analysis. The 'no-ROP'
group acted as normal control. Group 1 was further subdivided into 1A (threshold ROP), 1B (Aggressive Posterior ROP), 1C (hybrid ROP), and 1D (high-risk pre-threshold ROP).

RESULT:

Out of 436 eyes, Group 1, 2, and 3 had 238, 108, and 90 eyes, respectively. The mean rate of vascular outgrowth along with 95% confidence interval was 0.719 [0.703, 0.740], 0.612 [0.599, 0.638], and 0.490 [0.487, 0.520] DD/week, respectively, for babies with No-ROP, spontaneously regressed ROP, and treatment warranting ROP. More than 80% of eyes with a vessel growth rate of 0.54 to 0.57 DD/week or less required treatment.

CONCLUSION:

A retinal vascular growth of 0.54 DD/week or less could predict treatment requirements in babies with ROP.

TRANSLATIONAL RELEVANCE:

Rate of vascular growth could predict treatment requirement in ROP.

TEXT

INTRODUCTION

Retinopathy of Prematurity (ROP) is a disorder of immature retinal vasculature. Up to 12 weeks of fetal life, the developing retina is supplied principally by the blood vessels from the developing hyaloid system and a contribution from the choroidal vasculature. Major retinal arteries begin from the center of the optic disc at 16 weeks of gestation and grow peripherally at a rate of 0.1 mm per day. 1 It is also known that the internal vascular plexus of the retina grows 0.094 – 0.1 mm/day2 from 28 weeks of gestational age; this is equivalent to a vascularization rate of 0.7 mm/week or approximately 0.7 DD/week, taking mean horizontal optic diameter as one mm. 4,5,6 Abrupt stoppage of retinal vascularization in response to relative hyperoxia constitutes phase 1 of ROP. 7 Various systemic and ocular factors are known to affect the extent and severity of ROP. 8,20 These
include prematurity, low birth weight, collateral health issues (poor weight gain, sepsis, respiratory distress, apnea), excessive unmonitored oxygen supplementation, etc. \(^8\)\(^{20}\) Slow vascular growth has been reported to be an important cause for disease recurrence in babies treated with intravitreal bevacizumab (IVB) for ROP. \(^2\) ROP does not require treatment in every stage. The retinopathy does not reach the treatable stage suddenly. The follow-up examination interval depends on the severity of retinopathy, including the stage, location, and presence of plus or pre-plus components besides the postmenstrual age (PMA) and systemic status. \(^22\)\(^{26}\) The growth rate of retinal vessels in babies with ROP has not been studied enough (Medline search). \(^27\) In the present study, we analyzed the rate of vascular growth vis-à-vis the treatment decision in babies with variable ROP severity to determine if this biological marker could help in the decision-making for treatment.

METHOD

This retrospective study was conducted at a tertiary eye care center serving patients from Eastern India. All the prematurely born babies diagnosed with ROP of various degrees and the retina imaged with good image clarity were included in the study; the study period was from January 2010 to December 2019. Good retina image clarity was defined as the one where the optic disc and vascular endings were visible clearly for calculation. Those with insufficient or unclear images, short follow-ups, stage 4 and 5 ROPs were excluded. The institutional review board approved the study, and it followed the Declaration of Helsinki in research involving human subjects. The eye examinations and fundus imaging were done after written consent from the parents/guardian about imaging and possible use of the anonymized images for teaching and research.

Two pediatric retinal imaging devices were used- RetCam (Clarity Medical Systems, Pleasanton, California) and 3netra neo Digital Wide-field imaging system (Forus Health
Pvt Ltd, Bengaluru, India). When needed, the images were enhanced with a red-green image enhancement option available with the device (Figure 1).

The retinal imaging in these babies was as per the institute protocol. In brief, fundus images of most babies with ROP of any degree (and some of the babies with prematurity but no ROP) are obtained after informed and signed consent of the parents. The protocol allows obtaining at least basic images covering disc and macula, superior, inferior, superotemporal, inferotemporal, superonasal, inferonasal quadrant as far as possible. The babies were imaged every time they returned for a review. The interval varied from 1 to 6 weeks. The last follow-up varied depending on the time the disease regressed. The majority of the babies were evaluated as ambulatory care. We regularly imaged babies before and after laser procedures; these images were analyzed in the study. Among the multiple visits, we included the last visit image where the disc and the end of blood vessels were imaged simultaneously within a single field. In this study, the images obtained and archived as a part of patient care were analyzed. In group 1 with treatable ROPs, the calculations were done on the images taken on the day of or within a week before treatment.
All the measurements on the images were done from the mid-point of the nasal or temporal margin of the optic disc. The average optic disc horizontal width was taken as 1.05 mm as per the previous reports. 4,5,6 Retinal arteries start from the optic disc at 16 weeks of gestational age, grow at 0.1 mm per day,27 and probably reach the optic disc margin at 17 weeks. This presumption was made from the published report of vessel growth of 0.7 Disc diameter (DD) / week after 20 weeks of gestational age (GA). 27 We used the caliper option available with the imaging device in the case of RetCam (Figure 2) and a manual measuring scale in the 3 netra neo Digital Wide-field imaging system. The PMA (defined as the sum of gestational age and number of days elapsed since birth) in weeks was recorded at the measurement point. The following formula calculated the speed of vascular outgrowth (S) in disc diameter per week: “S=(A/D)/(P-17)” where “A” is the radial distance of the end of blood vessels from the middle of the disc margin, “D” is the horizontal disc diameter, and ‘P’ is the PMA at time of the rate calculation.
We calculated the vascular growth along the superotemporal and inferotemporal quadrants (STQ, ITQ), superonasal and inferonasal quadrants (SNQ, INQ), horizontal nasal (HNQ), and horizontal temporal (HTQ) quadrant, one or more for each eye (total of 6 or fewer measurements per eye). But most of the time, the images were clearer, and calculations could be done most often in superotemporal (428 out of 436 eyes) followed by inferotemporal (379 out of 436 eyes) followed by horizontal temporal quadrant (345 out of 436 eyes).

The babies were divided (Table 1) into Group 1 (Treatment warranting ROP) and Group 2 (spontaneously regressed / low-risk pre threshold ROP). All the classifications were done as per the CRYOROP, ICROP revised, and ETROP study.28, 29

Group 1 was further sub-divided (Table 1) into 1A (threshold ROP), 1B (Aggressive PosteriorROP), 1C (hybrid ROP), and 1D (high-risk pre threshold ROP). [“Hybrid ROP” refers to cases having ridge tissue, similar to staged ROP + flat new vessels, simulating APROP, in the same eye, described by Sanghi et al.30]

Babies born prematurely with an immature retina but did not develop ROP until the last visit were considered controls (Group 3). We excluded babies beyond 38 weeks PMA from the normative data calculation; the terminal ends of the retinal vessels in these babies’ images were difficult to appreciate. Since the horizontal disc diameter was used as the calculation unit in the study, we were aware of the possibilities of difference among different subgroups and consequent bias. So, we calculated the average disc size among the various groups and looked for any statistical difference.

The GA, BW, PMA, and retinopathy status are shown in Table 2. The ROP screening examinations had been done by multiple ROP specialists earlier. But the images were read and analyzed retrospectively by only three of them. The average and range of weekly vascular growth rates were measured for all groups and subgroups by two examiners separately (SP, AP); they had at least one year of experience diagnosing and managing
<table>
<thead>
<tr>
<th>Groups (251 babies,436 eyes)</th>
<th>Description</th>
<th>STQ (n)</th>
<th>ITQ (n)</th>
<th>HTQ (n)</th>
<th>SNQ (n)</th>
<th>INQ (n)</th>
<th>HNQ (n)</th>
<th>All Quadrants together</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Treatable ROP</td>
<td>0.522 ±0.13 6 (236)</td>
<td>0.51 ±0.13 4 (131)</td>
<td>0.4 ±0.08 75 (19)</td>
<td>0.31 ±0.08 5 (103)</td>
<td>0.2 ±0.08 2 (99)</td>
<td>0.490 ±0.12 1 (1)</td>
<td></td>
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</tr>
<tr>
<td>Group 1 n= 136 babies, 238 eyes</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1A Threshold ROP (37 babies, 64 eyes)</td>
<td>0.480 ±0.10 1 (63)</td>
<td>0.47 ±0.10 5 (091)</td>
<td>0.4 ±0.08 44 (14)</td>
<td>0.3 ±0.08 3 (01)</td>
<td>0.23 ±0.08 3 (165)</td>
<td>0.1 ±0.08 0 (7)</td>
<td>0.461 ±0.12 3 (1)</td>
<td></td>
</tr>
<tr>
<td>1B APROP (31 babies,59 eyes)</td>
<td>0.432 ±0.10 4 (59)</td>
<td>0.42 ±0.10 7 (111)</td>
<td>0.3 ±0.08 43 (95)</td>
<td>0.3 ±0.08 84 (15)</td>
<td>0.32 ±0.08 6 (104)</td>
<td>0.2 ±0.08 2 (94)</td>
<td>0.386 ±0.10 4 (16)</td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>Condition</td>
<td>Babies</td>
<td>Eyes</td>
<td>Mean</td>
<td>SD</td>
<td>Max</td>
<td>Min</td>
<td></td>
</tr>
<tr>
<td>-------</td>
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<td>-----</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>1C</td>
<td>Hybrid ROP (16 babies, 28 eyes)</td>
<td>0.538 ±0.132 (28)</td>
<td>0.512 ±0.126 (26)</td>
<td>0.42 ±0.61 (23)</td>
<td>0.30 ±0.63 (23)</td>
<td>0.32 ±0.63 (23)</td>
<td>0.2 ±0.32 (23)</td>
<td>0.480 ±0.422 (23)</td>
</tr>
<tr>
<td>1D</td>
<td>HRPTH ROP (52 babies, 87 eyes)</td>
<td>0.610 ±0.124 (86)</td>
<td>0.602 ±0.118 (85)</td>
<td>0.51 ±0.71 (76)</td>
<td>0.4 ±0.4 (76)</td>
<td>0.30 ±0.6 (76)</td>
<td>0.3 ±0.28 (76)</td>
<td>0.592 ±0.329 (76)</td>
</tr>
<tr>
<td>Group 2 (64 babies, 108 eyes)</td>
<td>Spontaneously regressed ROP</td>
<td>0.632 ±0.105 (105)</td>
<td>0.613 ±0.104 (96)</td>
<td>0.5 ±0.89 (97)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.612 ±0.106 (97)</td>
</tr>
<tr>
<td>Group 3 (51 babies, 90 eyes)</td>
<td>NO ROP</td>
<td>0.721 ±0.090 (87)</td>
<td>0.705 ±0.093 (51)</td>
<td>0.7 ±0.31 (57)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.719 ±0.093 (57)</td>
</tr>
</tbody>
</table>
ROP and in the imaging devices used in the study. A third examiner (TRP, ROP specialist with ten years of experience in ROP care) masked the treatment details, cross-checked the measurements, and his decision on the acceptance of one of the two measures in case of a disagreement was final. The examiners were given only one image per eye to do the calculations without showing the images in the other visits. The last follow-up image showing the optic disc and the end of the blood vessel together was selected for Groups 1 and 2. The same was also selected for Group 3 from the images taken on the day or within one week before treatment. We analyzed the inter-observer (between Observer 1 and 2) agreement in calculating the growth rate of blood vessels. The average rates were calculated for the two test groups (Group 2 and 3) and the control group (Group 1). An intragroup comparison was made, and their statistical significance was calculated (Table 1). Each eye's vascularization rate was arranged from lowest to highest value irrespective of the retinopathy and treatment. Finally, we calculated the strength of the correlation of vascular outgrowth rate with the treatment requirement. We used the ETROP guideline for treatment decisions. The ROP specialist (TRP) decided on the modality of therapy either alone or in combination and included retinal laser, intravitreal anti-vascular endothelial growth factor injection, or surgery.

STATISTICS:

The data were analyzed with SPSS V.21.0 (SPSS Inc, Chicago, IL, USA). Student’s t-test was applied to compare the average speed of vascularization in subjects with and without ROP in different quadrants. The mean, median, range of GA, BW, and PMA measurements in different groups was calculated. The average vascular growth in groups 1 and 2 was compared with the normative control, and the significance of the difference was estimated. The intraclass correlation coefficient test was used to assess the reliability of the observations made by observers 1 and 2. The p <0.05 was taken as statistically significant. The receiver operating characteristic (ROC) curve and the area under the curve (AUC)
ROP-Retinopathy of Prematurity, SD-Standard deviation, Post menstrual age is defined as a sum of gestational age and number of days elapsed since birth.

<table>
<thead>
<tr>
<th>Treatment Required</th>
<th>STQ</th>
<th>ITQ</th>
<th>HTQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interobserver correlation</td>
<td>95% Confidence interval</td>
<td>Interobserver correlation</td>
<td>95% Confidence interval</td>
</tr>
<tr>
<td>Single Measures</td>
<td>0.9664</td>
<td>0.9593 to 0.9722</td>
<td>0.7789</td>
</tr>
<tr>
<td>Average measures</td>
<td>0.9829</td>
<td>0.9792 to 0.9859</td>
<td>0.8757</td>
</tr>
</tbody>
</table>

HTQ - Horizontal temporal quadrant; ITQ-Inferotemporal quadrant; STQ-Superotemporal quadrant

Values less than 0.5 are indicative of poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.9 indicate good reliability, and values greater than 0.90 indicate excellent reliability.
APROP-Aggressive Posterior ROP, HNQ-Horizontal nasal quadrant, INQ-Inferonasal quadrant, HRPTH ROP-High Risk Prethreshold Retinopathy of Prematurity, HTQ-Horizontal temporal quadrant, ROP-Retinopathy of Prematurity, SNQ- Superonasal quadrant, STQ-Superotemporal quadrant

Table 2. Gestational Age (GA), Birth weight (BW) and Post Menstrual age (PMA) at calculation of babies within 3 sub groups in the present study

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Treatable ROP as a whole (Gr 1)</th>
<th>Subgroup 1A (Threshold)</th>
<th>Subgroup 1B (APROP)</th>
<th>Subgroup 1C (Hybrid)</th>
<th>Subgroup 1D (HRPT H)</th>
<th>Spontaneous Regression (Gr 2)</th>
<th>NO ROP (Gr 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>± 1.97</td>
<td>± 1.98</td>
<td>± 1.48</td>
<td>± 2.09</td>
<td>± 2.09</td>
<td>± 2.03</td>
<td>± 2.17</td>
</tr>
<tr>
<td>BW in g</td>
<td>640-2100</td>
<td>640-1900</td>
<td>850-1700</td>
<td>1000-1900</td>
<td>840-2100</td>
<td>700-2500</td>
<td>900-2400</td>
</tr>
<tr>
<td></td>
<td>(Range, Avg±SD)</td>
<td>(Range, Avg±SD)</td>
<td>(Range, Avg±SD)</td>
<td>(Range, Avg±SD)</td>
<td>(Range, Avg±SD)</td>
<td>(Range, Avg±SD)</td>
<td>(Range, Avg±SD)</td>
</tr>
<tr>
<td></td>
<td>626±1.64.56</td>
<td>1218.9±290.57</td>
<td>1210.3±205.11</td>
<td>1319.2±265.71</td>
<td>1309.1±305.85</td>
<td>3±363.69</td>
<td>4±324.45</td>
</tr>
<tr>
<td></td>
<td>±292.56</td>
<td>±8290.57</td>
<td>±205.11</td>
<td>±265.71</td>
<td>±305.85</td>
<td>±69</td>
<td>±95</td>
</tr>
<tr>
<td></td>
<td>PMA in wks at calculation (Range, Avg±SD)</td>
<td>29-44.57</td>
<td>31-41.71</td>
<td>33-39.14</td>
<td>31-44.57</td>
<td>32.85-41</td>
<td></td>
</tr>
<tr>
<td></td>
<td>36.52±2.37</td>
<td>35.06±2.14</td>
<td>35.74±2.13</td>
<td>36.73±3.02</td>
<td>38.65±2.92</td>
<td>37.49±1.72</td>
<td></td>
</tr>
<tr>
<td></td>
<td>±2.29</td>
<td>±3.02</td>
<td>±2.92</td>
<td>±1.72</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
were used to evaluate the predictive values, and determine the cut-off point in vascularization speed as a predictor of treatment need.

RESULTS

This study recruited 233 babies (bilateral: 203 and unilateral: 30) and 436 eyes that consisted of 238 eyes (n= 136 babies) in group 1 (treatment warranted), 108 eyes (n=64 babies) in group 2 (spontaneously regressed), and 90 eyes (n=51 babies) in group C (no-ROP) (Table 1). The subgroup of Group 1 was as follows: 1A (threshold ROP) 64 eyes; 1B (Aggressive Posterior ROP) 59 eyes; and 1C (hybrid ROP) 28 eyes; 1D (high-risk pre-threshold ROP) 87 eyes. There were 18 babies with each eye falling in a different group. The GA, BW, and PMA calculations of babies in each group are presented in Table 2. Out of 436 eyes, the measurements could be easily made in 428 (98.1%), 376 (86.2%), 344 (78.8%), 20 (4.0%), 17 (3.8%) and 22 (5.0%) eyes in STQ, ITQ, HTQ, SNQ, INQ, and HNQ respectively. The examiners succeeded in making calculations in STQ more often than the other quadrants. The inter-observer (between Observer 1 and 2) agreement in the calculation of the rate of growth of blood vessels was considered excellent in the STQ (0.982; 95% Confidence Interval, CI [0.079-0.985]) and good in the ITQ and HTQ (Table.3). The average rate of vascular growth (average of the rates in different quadrants) was 0.719 + 0.09, 0.612 + 0.10, and 0.49 + 0.12 DD/week in group 3 (No ROP), in group 2 (Spontaneously regressed), and in group 1 (treatable ROP) eyes respectively (Table 1 and Figure 3). The rate was lowest in subgroup1B, followed by groups A, C, and D. We observed the average horizontal disc diameter (the numerator for speed calculation in the study) of the eyes imaged with Ret Cam was not statistically different (p=0.069) between the three groups (58.98, 61.08, and 58.9 RetCam units for group 1,2, and 3 respectively).

In babies with treatment warranting ROP (Group 1), the vascular growth rate was lower in the nasal than in the temporal quadrant (Table 1). It was lowest in the HNQ (0.22 DD/week) and highest in the STQ (0.52 DD/week). The vascular growth rate in the HNQ was
Table 4. Receiver operating characteristic curve of STQ, ITQ and HTQ for predicting requirement of treatment

<table>
<thead>
<tr>
<th>Treatment Required</th>
<th>STQ</th>
<th>ITQ</th>
<th>HTQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area under the ROC curve (AUC)</td>
<td>0.817</td>
<td>0.791</td>
<td>0.819</td>
</tr>
<tr>
<td>Standard Error</td>
<td>0.0202</td>
<td>0.0232</td>
<td>0.0229</td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>0.777 to 0.853</td>
<td>0.747 to 0.831</td>
<td>0.774 to 0.858</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cut off</td>
<td>=0.569</td>
<td>=0.578</td>
<td>=0.542</td>
</tr>
<tr>
<td>Sensitivity (95% CI)</td>
<td>66.95% (60.6 - 72.9%)</td>
<td>73.71% (67.5 - 79.3%)</td>
<td>67.37% (60.2 - 74.0%)</td>
</tr>
<tr>
<td>Specificity (95% CI)</td>
<td>82.29% (76.1 - 87.4%)</td>
<td>71.23% (63.2 - 78.4%)</td>
<td>83.66% (76.8 - 89.1%)</td>
</tr>
<tr>
<td>PPV (95% CI)</td>
<td>82.3% (76.1 - 87.4%)</td>
<td>80.3% (74.3 - 85.4%)</td>
<td>83.7% (76.8 - 89.1%)</td>
</tr>
<tr>
<td>NPV (95% CI)</td>
<td>66.9% (60.6 - 72.9%)</td>
<td>63% (55.2 - 70.4%)</td>
<td>67.4% (60.2 - 74.0%)</td>
</tr>
<tr>
<td>Diagnostic accuracy</td>
<td>73.83%</td>
<td>72.75%</td>
<td>74.63%</td>
</tr>
</tbody>
</table>
43.48% of the rate of vascular growth in the STQ and 47.7% of the rate of vascular growth in the HTQ. In the spontaneously regressed and No-ROP group, we did not have enough measurements in the nasal quadrants to compare the speed with the temporal quadrant. The ROC showed that the rate of vascular growth was a significant predictor of the requirement of treatment at a cut-off value of d"0.569(STQ), d"0.57 (ITQ), and d"0.542(HTQ) with a chance of correctly predicting the requirement of treatment in 81%, 79% and 81% of cases respectively (Table 4 and Figure 4).

DISCUSSION

Retinopathy of prematurity has classically been described as a biphasic disease where the events start with delayed retinal vascular growth, resulting in a peripheral avascular retina (Phase 1). Later, vaso-proliferation (intravitreal angiogenesis) can occur at the junction of the avascular and vascularized retina (phase 2). In addition to prematurity, low birth weight, possible genetic factors, other factors (such as extent and duration of oxygen supplementation, postnatal weight gain, sepsis, hyaline membrane disease, cerebral hemorrhage, exchange transfusion, intubation for ten days or longer) also play important roles in the vascular development in prematurely born infants. A slow rate of retinal vascularization causes a larger avascular retina persisting for a longer period resulting in a greater VEGF load with an increase in the severity of retinopathy. The rate of vascularization is a quantifiable observation. De Larrey et al. have evaluated its efficacy in predicting the requirement of treatment using Indirect ophthalmoscopic evaluations. They showed that the rate of temporal retinal vascularization was significantly higher in no ROP (0.73 ± 0.22 DD/week) than in stage 1 (0.58 ± 0.22 DD), stage 2 (0.46 ± 0.14 DD/week) and stage 3 ROP (0.36 ± 0.18 DD/week). Following a study in 185 babies, they concluded that the slower rate of temporal retinal vascularization could alert a clinician of treatment need. The present study was conducted on a larger sample of patients; we measured the vascular growth in different quadrants around the optic disc, compared the speed of vessel development in ROP subtypes (helps treatment
decision in a real-life situation), and also used newer technology such as the red-green enhancement of the images, when required (easier identification of the course and termination of the artery). We used two observers to assure the reproducibility of the results, and compared it with an ROP expert's final treatment decision.

In our study, the average vascular growth rate in babies without ROP (group 3) was 0.719 ± 0.093DD/week and was similar to two earlier reports. In our analysis, the vascular growth rate was at least 20% slower in babies who needed treatment compared to those who did not (0.54 to 0.56 DD/week versus 0.72 DD/week). The examiners measured the speeds more easily and more often superotemporally and preferred this quadrant over other quadrants in the speed of vascular growth calculation.

ROP has been described to have nasal-temporal asymmetry. Gallaghar et al. report that at any given point, the retinopathy tends to be 2 to 3mm closer to the disc nasally than temporally. Nissenkorn et al. and Fielder et al. observed that ROP develops in the nasal retina about two weeks earlier than in the temporal retina. The reasons for this asymmetry in both time and location are unclear. The distance of disc to nasal ora (18.5 mm) is shorter, and it is 78.7% of the distance of disc to temporal ora (23 - 24 mm) long. However, the rate of vascular growth along the horizontal nasal quadrant, as seen in subjects with ROP in this study, was less than 50% of that in the temporal quadrant. This would mean that the distance between the optic disc to ora serrata is shorter nasally than temporally, and the speed of vascular growth is disproportionately less nasally than temporally. As a result, one should expect a larger avascular retina nasally than temporally. This could partly explain the naso-temporal asymmetry in ROP. While we have not used the present study's information prospectively, it suggests that a slower vascular growth rate should alert the treating ROP specialist for closer follow-up of these babies with extra attention to the correction of systemic risk factors, if any. Our study's results also prompt us to pay an additional weightage to the nasal quadrant while examining an eye for retinopathy of prematurity.
This study is not without limitations. The measurements of the optic nerve and vascular outgrowths were done on a flat laptop screen, while in reality, the optic nerve head lies on a curved surface, and retinal blood vessels travel on a curved surface. In an inclined image, the optic nerve dimension could be different. We did not have an easy way to calculate the distance of the end of the blood vessels along the vessel wall. So the measurements are actually along the chord length, and it is approximate to the actual length and velocity. Exact measurements of the end of the retinal blood vessels from disc margin without fundus fluorescein angiography (FFA; currently, we do not have it) is another limitation. FFA has been shown to improve visualization of the peripheral vasculature not easily captured by color fundus photography. We tried to circumvent the limitation by using red-free image enhancement that aids in better identify the blood vessels. Speed of vascularisation in any quadrant normalized by the optic nerve - ora serrata distance in that quadrant could have supported our claim that the speed is disproportionate in the nasal versus temporal quadrants. Unfortunately, we did not have an ultra-wide field pediatric retina imaging device that could image optic disc and ora serrata in one imaging field. Making a composite image from the posterior pole images and images of the peripheral retina up to ora serrata had its limitations of introducing errors. The problem of image magnification was overcome by using ratios of distance with the disc diameter as the unit of measurement instead of the absolute values. This is a ratio (number of disc diameters per week) and is unaffected by any magnification factor. This was further supported because there was no statistical difference in the individual horizontal disc diameter for measurement (p=0.069). The rate of vascularization could be different in different quadrants measured in the same subject and same time. This was overcome by measuring in specific quadrants in every eye. A good inter-observer correlation coefficient (Table 3) and a uniform time point of calculation (last follow-up visit) further reduced the variabilities.
We had our surprises. Contrary to our expectation that vascular growth rate in eyes with hybrid ROP would be similar to APROP and lower than threshold ROP, it was instead faster. We realize that the eyes with hybrid ROP at times could have large vascular loops and could spread to an anterior zone even though the retina within the loop is avascular.30 In the study, the calculations were done at a fixed point of time, assuming that the vascularization rate was uniform over the period studied. This might not be true. The vascular growth depends on many systemic factors that change over time, and so would be the speed. This calls for a prospective study to document the weekly growth in eyes under observation for ROP. Once validated, this parameter would be easily adaptable to clinical settings.

CONCLUSION

There was a good correlation between the weekly rate of vascular growth and the decision to treat babies with ROP in this study. The vessel growth rate was inversely proportional to the disease severity and was lowest in the APROP group. The growth rate nasally was slower than on the temporal side. Measuring vascular growth in the superotemporal was easier than in other quadrants.

ACKNOWLEDGMENT:

Authors acknowledge the help of Mrs. Bhawna Garg in the statistics related to the manuscript.

REFERENCES


27. Solans Pérez de Larrau AM, Ortega Molina JM, Fernández JU, et al. Retinal vascular speed <0.5 disc diameter per week as an early sign of retinopathy of prematurity.


**LEGENDS TO FIGURES**

Figure 1 (Left) Color fundus image of the left eye taken with 3 netra neo Digital Wide-field imaging system (Forus Health Pvt Ltd) showing few tortuous vascular loops around optic disc. Nasally they hardly extend beyond 1.5 Disc diameter from nasal border of the optic disc. (Right) Same eye after red green enhancement making the blood vessels stand out with better clarity.

Figure 2. Snap shot image showing the method of measurement of vascular growth done on the laptop screen and the calliper option available with RetCam (Clarity medical Inc). The eye shown here shows threshold retinopathy of Prematurity (ROP) in zone I. The disc dimensions are measured both horizontally and vertically and the ends of the blood vessels are measured in supero, infero and horizontal temporal quadrants.

Figure 3. Diagram showing the average speed of retinal vascularization in babies with Retinopathy of Prematurity of varying severity.

Figure 4. The Receiver operating characteristic curve (ROC) to find out area under the curve and cut-off point of vascular growth predicting a decision to treat. ROC curves above the diagonal line are considered to have reasonable discriminating ability to predict requirement of treatment. The Discriminatory power of the rate of Vascular growth (Area under curve 0.819, 0.791, 0.819, 95% confidence interval-66.95, 73.71 and 63.37 respectively for STQ, ITQ and HTQ) was acceptable rate of vascular growth was a significant predictor of requirement of treatment at a cut off value of d"0.569 (STQ), d"0.57 (ITQ) and d"0.542 (HTQ) with a chance of correctly predicting the requirement of treatment in 81, 79 and 81% of cases respectively.

Table 1. Speed of vascular outgrowth in eyes with treatable, spontaneously regressed and No ROP
Table 2. Gestational Age, Birth weight and Post Menstrual age at time of measurements in babies within the three sub groups in the present study

Table 3. Inter-observer co-relation co-efficient between observer 1 and 2

Table 4. Receiver operating characteristic curve of supero, infero and horizontal temporal quadrant for predicting requirement of treatment
Interweaving Structural And Functional Findings In Mactel Type 2

Dr. Nishita Yadav, Dr. Apoorva Ayachit, Dr. Guruprasad Ayachit, Dr. Shrinivas Joshi

ABSTRACT

PURPOSE:

To study the correlation of multimodal imaging in macular telangiectasia (Mac Tel) with foveal function on multifocal electroretinogram (mfERG)

METHODS:

Eyes with non-proliferative Mac Tel diagnosed based on clinical examination, optical coherence tomography (OCT), autofluorescence (AF), fluorescein angiography (FA), OCT angiography (OCTA). Control group with normal eye exam included for multifocal electroretinogram. Staging of OCT, OCTA, AF and FA done in Mac Tel subjects. mfERG done in study subjects and controls. Correlation of imaging modalities and P1 amplitudes at fovea (ring 1) studied in terms of correlation co-efficient.
RESULTS:

Twenty nine eyes of 16 patients of Mac Tel and 25 eyes of 19 controls were included. BCVA was 0.38 ± 0.266 in study eyes and 0 in control eyes. On OCT it was observed that 41.4% Mac Tel eyes (n = 12) belonged to stage 3, 33.9% (n = 11) eyes belonged to stage 2 and 20.7% (n = 6) eyes belonged to stage 1. AF- Stage 3 comprised of 75.9% eyes (n = 22); 4 eyes belonged to stage 2 and 3 eyes to stage 1. On FA, 18 eyes belonged to stage 3 (62.1%); stage 2 was seen in 1 (3.4%) eye and stage 1 was seen in 10 (34.5%) eyes. There was decrease in P1 amplitudes from R1 (p < 0.001), R2 (0.001), R3 (< 0.001) and R4 (0.001) in Mac Tel eyes compared to control eyes but not in R5 (p 0.785).

SD- OCT had positive correlation with FAF (CC 0.747, p < 0.001) FFA (CC 0.775, p < 0.001) and R1P1 (CC 0.682, p < 0.001). With OCTA there was no significant correlation (CC 0.318, p 0.093). There was positive and significant correlation of OCT (0.682, < 0.001), OCTA (0.379, p 0.042) AF (0.635, p < 0.001) and FA (0.495, p < 0.006) with R1P1.

CONCLUSIONS:

Existing multimodal imaging systems can be reliable indicators of foveal function as on mfERG.

KEYWORDS

Macular telangiectasia, OCT, OCTA, autofluorescence, mfERG

INTRODUCTION

Macular telangiectasia type 2 (Mac Tel type 2) is a bilateral neurodegenerative disease affecting muller cells in the macula. The age of onset is typically between 40 to 50 years.¹ Symptoms include reduced reading vision, scotoma and metamorphopsia.² Loss of best corrected visual acuity (VA) is very gradual and is a late symptom because of relative
foveal sparing in the early stages of the disease. Multimodal imaging techniques have identified structural changes in early Mac Tel much before VA is affected. Fluorescein angiography (FA), autofluorescence (AF), confocal blue reflectance (CBR), multicolor (MC) imaging, optical coherence tomography (OCT), OCT angiography (OCTA) have provided data on structural changes in Mac Tel and thus provided insight into its pathogenesis. Although these structural details and their functional implications have been noted in terms of BCVA and microperimetry, correlation of these imaging modalities with multifocal electroretinogram (mFERG) has not been studied.

METHODS

The study was carried out in patients attending the retina services of a tertiary referral centre in south India. Macular telangiectasia was diagnosed on basis of slit lamp biomicroscopic examination, AF, spectral domain (SD) OCT, FA and OCTA.

STUDY DESIGN AND SAMPLE

This was a cross sectional study conducted from May 2017 to May 2019. Twenty nine eyes of 16 macular telangiectasia patients and 25 eyes of 19 normal patients were recruited in the study. Subjects enrolled in the study were explained about the imaging modalities being utilized and informed consent was obtained. Ethical approval was obtained from the Institutional Review Board. The study was conducted in accordance with the ethical standards laid down in the declaration of Helsinki.

All control eyes had BCVA of 6/6 and had spherical equivalent of less than 2 diopter sphere (DS). Both study eyes and control eyes had clear media. Eyes with neovascularization, glaucoma and other optic nerve diseases were excluded.

Clinical staging was done in accordance with Gass et al viz. stage 1- parafoveal graying, stage 2- graying, stage 3- right angled venule, stage 4- pigment plaques, stage 5- choroidal neovascular membrane (CNVM).
SD-OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany) was done and central macular thickness was noted at the foveal centre as distance from the ILM to the RPE. Spectral-domain OCT was performed with a scan angle of 20° in the infrared photography plus OCT mode with the automatic real-time mode switched on.

The distance between 2 B-scans was 30 microns.

Temporal, nasal, and foveal loss of ellipsoid zone was noted. The presence of empty spaces and intraretinal pigment with back shadowing also were noted. The horizontal lengths of ellipsoid zone disruption and external limiting membrane disruption in the line scan passing through the fovea were measured manually using the caliper function in-built in the imaging system.

OCTA scans were carried out (high speed Protocol 15*15) with a scan angle of 10° and a pattern size of 2.9 * 2.9 mm. Distance between B-scans was 11 microns. In case of macular thinning, loss of retinal architecture, or both; manual segmentation was carried out in 5 to 7 scans and semi-automated scans were procured and analysed.

AF and FA were both performed on the Spectralis Heidelberg with both 30- and 55-degree scans as high resolution scans. FA was performed using 3 cc of 20% fluorescein dye.

AF was classified in accordance with Wong et al. OCT, OCTA and FA were classified in accordance with Toto et al (table 1).

All macular telangiectasia patients and normal subjects underwent multifocal ERG (RETIscan, Roland Consult, Germany). The International society for clinical electrophysiology of Vision (ISCEV) guidelines were followed. Before recording, pupils were dilated using 1% tropicamide and 2.5% phenylepinephrine eye drops. The stimulus matrix consisted of 61 scaled hexagonal elements displayed on a monitor and a central red square was used as a fixation target and good fixation was ensured throughout. The
TABLE 1

Staging of imaging modalities - reproduced from Toto et al.

<table>
<thead>
<tr>
<th>Staging modality</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCT</td>
<td>A break in the EZ, with inner and outer retinal cysts temporal to the foveal center</td>
<td>EZ break reaching the foveal center with central outer cysts, and inner cysts involving temporal, central and nasal side; collapse of outer plexiform layer towards choroid. Hyperreflective intraretinal lesion due to pigment plaques is visible.</td>
<td>Only minor retinal cysts remain, EZ break involves the nasal side. The &quot;collapse&quot; of the layers is extensive. Hyperreflective intraretinal pigment plaques seen</td>
<td>Signs of outer retinal neovascularization with activity.</td>
</tr>
</tbody>
</table>
radius of stimulus array subtended at a viewing distance of about 27 cm, and each element was independently alternated between black and white stimuli.

Trace arrays at 61 location points of the first order kernel were analyzed for amplitude of 5 concentric rings (foveal R1, < 20 R2 5-100 R3, 10-150 R4 and >150 R5). The average amplitude P1 waves in all the rings were compared with the age matched normative data. Paracentral responses just temporal and nasal to the central element (element 30 and 32 in a standard 61-element array) were also individually analysed, and the relative difference between the temporal versus nasal amplitudes for each eye was also compared.

Grading of each imaging technique was performed independently by two retina specialists and results were comparable for inter-observer reliability. In case of discrepancy, the staging was arrived at by consensus. The results of grading were used to correlate between multimodal imaging and multifocal ERG. For purpose of correlation, the R1P1 amplitudes were divided into four quartiles. (Table 2)

<table>
<thead>
<tr>
<th>OCTA</th>
<th>Capillary anomalies (deep plexus and/or superficial plexus) in temporal fovea</th>
<th>Deep and/or superficial vascular plexus anomalies in temporal and nasal parafovea</th>
<th>Diffuse circumferential vascular anomalies in deep and/or superficial plexus</th>
<th>Neovascularization in outer retina</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAF*</td>
<td>Loss of foveal hypoAF</td>
<td>hyperAF at fovea and slight hyperAF parafoveal</td>
<td>Heterogeneous pattern AF</td>
<td></td>
</tr>
<tr>
<td>FFA</td>
<td>Temporal changes</td>
<td>Temporal and nasal changes</td>
<td>Full involvement</td>
<td>Signs of classic neovascularization</td>
</tr>
</tbody>
</table>

*Staging of AF by Wong et al
Data was entered in Microsoft excel data sheet and was analysed using SPSS 22 version software. Categorical data was represented in the form of frequencies and proportions and analyzed using chi square or Fischer’s exact test. Continuous data was represented as mean and standard deviation and paired t test was used for differences in patients and controls. Group wise analysis of individual SD-OCT findings was done to study their influence on mfERG and BCVA. p value of less than 0.05 was considered statistically significant. Spearman co-efficient was calculated to look for correlation between different imaging systems and mfERG.

<table>
<thead>
<tr>
<th>Macular telangiectasia type 2 stages</th>
<th>R1 P1 (n=29) in nV/deg2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>161.0 - 98.0</td>
</tr>
<tr>
<td>Stage 2</td>
<td>97.0 - 64.0</td>
</tr>
<tr>
<td>Stage 3</td>
<td>63.0 - 43.0</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Less than 42.0</td>
</tr>
</tbody>
</table>
RESULTS

DEMOGRAPHIC DATA

A total of 29 eyes of 16 patients and 25 eyes of 19 controls were included in our study. Mean age of patients was 57.14 ± 11.76 years and controls was 55.14 ± 10.73 years. There were 9 men and 20 women in the study group (controls – 13 females and 6 males). BCVA was 0.38 ± 0.266 in study eyes and 0 in control eyes.

Both eyes of 13 patients were included and one eye of three patients was chosen as the other eye in these patients had proliferative MacTel. At the time of study, the other eye in these three patients were treatment-naïve. Nine patients had diabetes and five had hypertension. None of the study eyes had diabetic retinopathy. Twenty four eyes were phakic and 5 were pseudophakic in the study group and all control eyes had crystalline lens.

In study eyes, greying of temporal parafovea was seen in all eyes, right angled venule were seen in 82.3% (n = 24).

On OCT it was observed that 41.4% (n = 12) belonged to stage 3 where as 37.9% (n = 11)) of eyes belonged to stage 2 and 20.7% (n = 6) eyes belonged to stage 1 (Table) Subretinal and intraretinal degenerative spaces were noted in 24.1% (n = 7) and 55.2% eyes (n = 16) respectively. Collapse sign was seen in 69% eyes (n = 20). The mean central macular thickness was 147.7 micrometre (µm).

AF- 22 eyes belonged to stage 3 (75.9%); 4 eyes belonged to stage 2 and 3 eyes to stage 1.

FFA- 18 eyes belonged to stage 3 (62.1%); stage 2 was seen in 1 (3.4%) eye and stage 1 was seen in 10 (34.5%) eyes. (Table 3)

Multifocal ERG – There was decrease in P1 amplitudes from R1 (p < 0.001), R2 (0.001), R3 (<0.001) and R4 (0.001) in Mac Tel eyes compared to control eyes but not in R5 (p
There was also asymmetry in P1 amplitude between temporal and nasal segments which was significant - Temporal (85.83 nanovolt) vs nasal (95.25 nanovolt)

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Stage 1 (n)</th>
<th>Stage 2 (n)</th>
<th>Stage 3 (n)</th>
<th>Stage 4 (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCT</td>
<td>6</td>
<td>11</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>AF</td>
<td>3</td>
<td>4</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>FFA</td>
<td>10</td>
<td>1</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>OCTA</td>
<td>7</td>
<td>6</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>mfERG</td>
<td>7</td>
<td>8</td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3- Distribution of eyes in individual stages of OCT, AF, FFA, OCTA and mfERG segment (p=0.043).

CORRELATION BETWEEN IMAGING MODALITIES AND MFERG:

SD- OCT had positive correlation with FAF (CC 0.747, p<0.001) FFA (CC 0.775, p<0.001) and R1P1 (CC 0.682, p<0.001). With OCTA there was no significant correlation (CC 0.318, p 0.093). AF staging correlated with all imaging except OCTA. FFA had positive correlation

<table>
<thead>
<tr>
<th>R1P1</th>
<th>SD</th>
<th>Mean R2P1</th>
<th>SD</th>
<th>Mean R3P1</th>
<th>SD</th>
<th>Mean R4P1</th>
<th>SD</th>
<th>Mean R5P1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study eyes</td>
<td>71.7</td>
<td>38.05</td>
<td>79.0</td>
<td>5.09</td>
<td>61.3</td>
<td>10.43</td>
<td>50.68</td>
<td>25.04</td>
</tr>
<tr>
<td>Control eyes</td>
<td>192.37</td>
<td>69.91</td>
<td>134.34</td>
<td>44.14</td>
<td>104.16</td>
<td>31.88</td>
<td>76.14</td>
<td>22.31</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.01</td>
<td>0.001</td>
<td>&lt;0.01</td>
<td>0.01</td>
<td>0.78</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4 Comparison of P1 amplitudes of R1, R2, R3, R4 and R5 between study eyes and control eyes. P1 amplitudes are in nanovolts (nV/ deg2)
<table>
<thead>
<tr>
<th></th>
<th>SD OCT staging</th>
<th>FAF staging</th>
<th>FFA Grading</th>
<th>OCTA staging</th>
<th>R1P1</th>
<th>R2P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spearman's rho</td>
<td>0.747*</td>
<td>0.775*</td>
<td>0.318</td>
<td>0.682*</td>
<td>0.22</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.093</td>
<td>&lt;0.001</td>
<td>0.244</td>
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<td></td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>29</td>
<td>29</td>
<td>29</td>
<td>29</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>0.747*</td>
<td>0.747*</td>
<td>0.237</td>
<td>0.635*</td>
<td>0.26</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.216</td>
<td>&lt;0.001</td>
<td>0.16</td>
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<td></td>
<td>*</td>
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<td>29</td>
</tr>
<tr>
<td></td>
<td>0.775*</td>
<td>0.747*</td>
<td>0.395</td>
<td>0.495*</td>
<td>0.15</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.034</td>
<td>0.006*</td>
<td>0.42</td>
<td>8</td>
</tr>
<tr>
<td></td>
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<td>*</td>
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<tr>
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<td>29</td>
<td>29</td>
<td>29</td>
<td>29</td>
<td>29</td>
<td>29</td>
</tr>
</tbody>
</table>
with all imaging modalities. All imaging modalities showed a positive correlation with R1P1 that was significant. (Table 5)

**Table 5- Correlation between imaging modalities and mfERG Expressed in Spearman's co-efficient**
DISCUSSION

Until recently, FFA was the gold-standard for the diagnosis of Mac tel. However, the pathological changes in Mac Tel occur in the deeper capillary plexus as evidenced by OCTA studies. There is a depletion of intraretinal structure causing degenerative spaces and/or macular thinning. The epicentre of these changes is in the temporal parafovea. Toto et al found strong correlations between OCTA and SD-OCT, early and late FFA. High correlations were also found between CBR and FFA. Moderate correlations were found between SD-OCT and FFA and also CBR. There was low correlation between FAF and CBR. This study concluded that OCTA had high correlations with established imaging techniques and suggested the use of OCTA as a non-invasive tool for detecting early Mac tel changes. Our study found positive correlation between OCT, AF and FFA. OCT and AF did not correlate significantly with OCTA. However there was high and significant correlation between imaging modalities and R1PQ. Pauleikhoff et al studied the correlation of vascular change patterns in terms vessel lengths, number of branches, number of vessel segments and fractal dimension with extent of EZ loss on SD-OCT. There was progressive reduction of number of vessel branches, vessel segments and fractal dimension values in both SVP and DVP that correlated with increasing EZ loss.

Structure-function correlation in Mac Tel has been attempted in the past by correlating macular pigment optical density (MPOD) and BCVA. Zeimer et al utilized a dual-wavelength system and classified MPOD into class 1- temporal parafoveal triangular segment of reduced MP, class 2- generalized reduction of foveal MPOD with central sparing, class 3- horizontally oval effacement of MP and rim of MP at 5-7 degrees eccentrically. They found that higher class of MPOD correlated with higher stages of Mac tel. There was also significant BCVA differences between class 1 and the higher classes. In a later work, Zeimer et al found the MPOD distribution into 3 classes showed strongest correlation with changes in the SVP.
Park et al assessed the correlation of OCTA-based foveal avascular zone (FAZ) area in SVP and DVP with BCVA in Mac Tel and controls. They found significant negative correlation between FAZ of SVP, DVP and BCVA in the study group. BCVA remains a subjective end-point for macular telangiectasia because the central fovea is affected only in the later stages. BCVA was not used as an end point in the clinical trial (phase 2) of ciliary neurotrophic factor for Mac Tel and EZ loss on OCT was chosen as the primary outcome. Microperimetry as a functional test has been studied in relation to Mac tel. Since microperimetry can test for sensitivity and assess extrafoveal visual loss, it has been used as an end-point in clinical trials of Mac Tel as a secondary outcome. However, challenges are test duration and requirement of good fixation. The test also needs intense concentration and skilled examiners thus limiting it to select patient groups. However, after the initial learning curve, high test-retest reliability has been found. Despite this, subtle losses of sensitivity in between testing areas can be missed. Besides, microperimetry is a tool that measures not just retinal physiology but is also influenced by the entire visual pathway.

Kihara et al developed a deep-learning network that could directly estimate retinal function from superpositions of high resolution OCT scans and microperimetry results. The predictions were used to create high-density enface sensitivity maps of the macula. In their study, they found that activation maps generated showed that the important structures identified were in the outer retina especially the ellipsoid zone. MFERG on the other hand is more objective because the first order kernel responses originate solely from the bipolar cells and photoreceptors.

There is limited literature on electrophysiology in Mac Tel. Normal ERG and EOG has been reported in case series ruling out generalized retinal and RPE dysfunction. Ledolter performed full-field ERG and pattern ERG in mac Tel eyes and suggested inner retinal dysfunction in rods and cones attributable to Muller cell dysfunction. Goel et al compared the mean P1 amplitudes and implicit time (IT) in R1 to R5 between Mac Tel
eyes and controls and found that mean P1 amplitudes were significantly decreased in Mac Tel eyes compared to controls in R1. The P1 amplitudes also decreased gradually from R1 to R5. This trend however was not seen in implicit time. They studied the correlation between BCVA, mFERG amplitudes and CMT. Although they noted a significant and negative correlation between BCVA and P1 amplitude and implicit time, the positive correlation of CMT and P1 was not significant.  

Narayanan et al stated there was a significant reduction in amplitudes as well as delay in implicit times of the waveforms in patients with type 2 Mac Tel in all the rings, compared to a matched normal population. The maximum reductions were seen in R1. They hypothesized that the reduction in amplitudes of waveforms, even in the peripheral rings, could be explained by the fact that telangiectatic vessels have been shown on fluorescein angiography even 2500 microns away from the fovea. Our study showed a reduction in P1 in rings 1 to 4 but not in R5.  

Mali Okada et al in their study stated that mFERGs showed preservation of the early N1 in R1 but selective reduction of the P1. The temporal paracentral response was also affected in half of the patients, with significant asymmetry between temporal and nasal responses. In their study, peripheral mFERG responses were unaffected and they concluded that Mac Tel is a localized disturbance of macular function, and uniquely provide evidence of an inner retinal site of dysfunction. They further stated that increase in the size of the EZ break area was significantly associated with decreasing central hexagon P1 amplitudes. Our study also showed statistically significant negative correlation between central R1 response with the length of EZ loss on OCT. Increasing length of the EZ break area was significantly associated with decreasing central hexagon P1 amplitudes. Thus the primary pathology in Mac Tel is post-photoreceptoral.  

CONCLUSION

To the best of our knowledge there is no other study correlating multimodal imaging
with cone function amplitude. We have developed an mfERG staging system for Mac Tel type 2. The clinical application of mfERG is limited by the lack of such equipment in many clinical centers. Positive correlation of R1 P1 amplitudes with existing multimodal imaging systems makes it possible to glean information about macular function from multimodal imaging.

DECLARATIONS

FUNDING:

No funding sources

CONFLICTS OF INTEREST:

The authors have no relevant financial or non-financial interests to disclose.

ETHICS APPROVAL:

The study protocol was approved by the Institutional Review Board (IRB) of M M Joshi Eye Institute and adhered to the tenets of the Declaration of Helsinki. Consent to participate: Informed consent was obtained from all patients before study inclusion.

AVAILABILITY OF DATA AND MATERIAL:

The datasets generated during the current study are available from the corresponding author upon request.

CODE AVAILABILITY:

Not applicable

REFERENCES:

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18. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6484597/


Comparative Study Of Success Of Various Techniques Of ILM Peel In Management Of RRD With PBR With MH

Dr. Prashant Keshao Bawankule

PURPOSE

To assess the anatomical and functional success in patients with rhegmatogenous retinal detachment (RRD) with proliferative vitreoretinopathy (PVR) e C1 with coexisting macular holes (MHs) using different management strategies.

MATERIALS AND METHODS

It is a prospective, nonrandomized, observational study in 23 eyes of 23 patients (male: female = 15:8) diagnosed with RRD with PVR e C1 with MH. Patients were divided into three groups according to the technique: Group 1: Pars plana vitrectomy (PPV) without internal limiting membrane (ILM) peel, Group 2: PPV with ILM peel, and Group 3: PPV with inverted ILM peel technique.

RESULTS

The closure of MH was confirmed on SD-OCT. Of the total 23 eyes, 19 patients had attached retina with closed MH during a follow-up period of 6 months. Out of four cases of recurrent retinal detachment (RD), three patients belonged to the no peel group and one to the ILM peel group. In no peel group, two patients had recurrence with re-opening of MH, and out of these two cases, one patient had additional break in the periphery.
However, two other cases, each from no peel and ILM peel group, had recurrence due to PVR changes in the periphery. Visual acuity (VA) improvement to LogMar d’1 is seen in 50%, 70%, and 85.7% in the no peel, ILM peel, and inverted flap technique, respectively.

CONCLUSION

The results suggest that ILM flap technique without encirclage band can be effectively applied to the treatment of MH with RD with more severe PVR changes and that the hole closure results in improved postoperative best-corrected VA.

KEYWORDS:

Internal limiting membrane peel, inverted internal limiting membrane peel, macular hole, retinal detachment

INTRODUCTION

About 2.5%–4% of cases of rhegmatogenous retinal detachment (RRD) have coexistent macular hole (MH),[1] and according to different studies, 53%–67%[1-2] of cases have associated proliferative vitreoretinopathy (PVR) at presentation. RRD with concomitant MH can typically occur in two scenarios. First, MH acts as a hole and leads to retinal detachment (RD) which is typically posterior but in rare cases can extend anteriorly. This scenario is usually seen in the pathological myopia cases[3] and is not associated with breaks in the periphery.[3]

In the second scenario, RD typically starts with break in the periphery and progresses posteriorly. Because of spreading of the subretinal fluid under fovea, it may cause stretching of retinal tissue, leading to MH formation.

The pathogenesis behind RRD with peripheral breaks with concomitant MH is not fully understood. There are various theories behind pathophysiology of RRD with MH. One theory is that posterior vitreous detachment (PVD) can put traction on central macula causing MH[3] (mechanism similar to that causes peripheral break). Another theory is similar to PVR process, i.e., peripheral break releases retinal pigment epithelial (RPE) cells, which attach to macular surface and contracts, leading to tangential traction and thereby MH formation.[2]
The principle to manage RRD with PVR is similar, i.e., relief of traction (by membrane peeling/retinotomy/relaxing retinectomy), closure of break(s), and tamponade. However, associated MH management is a point of debate. Although the principle of management of MH with RRD is similar to typical MH without concurrent RRD, challenges to repair hole in RRD are different. First challenge is fear of dye (used for staining internal limiting membrane [ILM]) gaining access to the subretinal space in a detached retina and so its potential toxicity. Another challenge is to peel ILM in the detached mobile retina. Various studies\(^4\) have demonstrated the use of Per Fluoro Carbon Liquid (PFCL) to flatten retina to aid in the ILM peel in such cases. However, in spite of all the maneuvers, every time, it is not possible to achieve ILM peel in such cases.

Various studies have reported various success rates with and without ILM peel. A study by Ryan et al.\(^5\) has shown increased success with ILM peel, while the study by Shukla et al.\(^6\) reported similar anatomical success with any of the techniques and better visual gain in the no peel group. However, these studies excluded cases with PVR > C. They also placed encirclage band in all cases and used silicon oil as a tamponading agent in majority of their cases. A study by Najafi et al.\(^1\) reported a recurrence rate of 27% in the ILM peel group while 50% in the no peel group in cases of significant PVR.

Studies have shown increased favorable surgical outcomes with inverted ILM flap technique in refractory MH\(^7\) and MH-RD.\(^8-10\) One study\(^11\) has studied the success of free ILM flap or inverted ILM peel flap in cases of paracentral breaks in RD.

No study has directly compared the success rate with no peel, ILM peel, and inverted flap (IF) technique. To our knowledge, ours is the first study that compared the surgical and functional success rates in cases of RRD with concurrent MH with different strategies, i.e., no ILM peel, ILM peel, and IF ILM peel in cases of PVR e”Grade C, and without concurrent use of encirclage band.

**MATERIALS AND METHODS**

**STUDY DESIGN**

This was a prospective, nonrandomized, observational study on 23 eyes of 23 patients of RRD with PVR e” C with concurrent full-thickness MH who underwent vitrectomy.
between July 2018 and October 2019 at a tertiary care center. All operations were performed by a single experienced vitreoretinal surgeon. The study was performed according to the ethical standards of the Declaration of Helsinki and approval from the ethics committee. Eyes were randomly distributed into three groups – Group 1: PPV with no ILM peel, Group 2: PPV with ILM peel, and Group 3: PPV with inverted ILM peel flap technique. For the purpose of the study, patients with RD secondary to MH (with no peripheral breaks), axial length >24 mm, recurrent RD, combined RD, and incomplete follow-up were excluded from the study. All patients had PVR stage ≤ C1. PVR staging was graded according to the updated classification of Retina Society Terminology Committee (1991). All patients underwent thorough preoperative ophthalmological examination, including best-corrected visual acuity (BCVA), slit lamp examination, and dilated indirect ophthalmoscopy examinations. The presence of MH was confirmed either before surgery with OCT [Figure 1a and b] or during surgery by direct examination [Figure 2a and b]. Demographic data and lens status at the time of surgery were recorded. SD-OCT (Zeiss) [Figure 3a-c] and fundus photograph [Figure 4] were done 1 month later to document the status of MH. BCVA and retinal status were recorded at 1 month, 3 months, and 6 months after the first surgery.

SURGICAL TECHNIQUE

In all cases, 23-gauge PPV with Alcon constellation was performed using a noncontact wide-angle viewing system (Oculus BIOM). Informed written consent was taken from the patients before surgery. Surgery was performed mostly under local anesthesia. Cannulae were placed 3 and 3.5 mm away from the limbus in pseudophakic and phakic patients, respectively. Core vitrectomy was done. Remaining adherent posterior hyaloid was removed by PVD induction using cutter. Membranes were peeled using peeling forceps. Base excision with scleral depression was done in all cases. No case received encircling/sclera buckle (SB). In Group 2 and 3, Internal Limiting Membrane (ILM) peel was done after staining with Brilliant blue dye (0.05%) by pinch and peel technique using ILM forceps (Grieshaber, Alcon) under PFCL. ILM was peeled at the macular area in Group 2. In Group 3, IF technique was done after peeling the ILM. PFCL was used to flatten the retina followed by PFCL–air. Drainage of the fluid was predominantly done...
through the peripheral break after flattening retina with PFCL till edge of the posterior most peripheral break. Residual fluid through MH was drained only in Group 1 and 2 with 41-gauge tapered extrusion needle (by Pricon). Endolaser was applied around the peripheral retinal tear and 360° to the vitreous base. Tamponading with silicon oil (1000 centistokes) was done in all cases.

Silicon oil removal was done at 3 months after the surgery in patients with attached retina and earlier in patients with recurrent detachment. The cause of recurrent RD in our study

Figure 1: (a and b) SD OCT preoperatively showing retinal detachment with macular hole

Figure 2: (a) Intraoperative fundus photograph before drainage of fluid (macular hole not seen). (b) Intraoperative fundus photograph revealing macular hole after drainage of fluid

was reopening of MH in two cases and peripheral PVR in two cases. Patients with recurrence due to re-opening of MH in the no peel group underwent ILM peel with
tamponading during re-surgery. Patients with recurrence in No peel group underwent membrane peel with tamponade during re-surgery. No belt buckle was done even in recurrent RD cases.

STATISTICAL METHODS

The baseline characteristics of the patients across three groups, i.e., ILM IF, ILM peel, and no ILM peel, were summarized according to the scale of measurement. The continuous variable such as age was expressed in terms of mean and standard deviation, and the significance of difference across groups was tested using one-way analysis of variance. The categorical variables such as gender, preoperative visual acuity (VA), and lens status were summarized as numbers and percentage, and the difference was tested using Pearson’s Chi-square test. The comparison of VA before and after treatment was compared using McNemar test. Further, the comparison of VA >1 across three treatment groups was carried out using Fisher’s exact test. The cumulative recurrence rates of RD were obtained as Kaplan–Meier plots [Figure 5] and were compared using log-rank test.

RESULTS

The descriptive statistics for 23 cases treated with ILM IF (n = 7), ILM peel (n = 10), and no peel (n = 6) are given in Table 1. The difference in the mean age of the patients across groups was statistically insignificant. In addition, the gender distribution and preoperative VA status of the patients across three treatment groups was insignificantly different. However, the lens status showed significant difference across groups (P < 0.0001), with 90% of the ILM peel-treated cases as pseudophakic and aphakic. The overall comparison of VA of cases before and after treatment across three groups revealed statistically significant difference with a P value of 0.0003 using McNemar test [Table 2]. Sixteen out of 23 cases (69.5%) with preoperative VA >1 (LogMar) had postoperative VA <1 (LogMar). Overall, there was a statistically significant improvement in the VA after treatment. Further, the comparison of postoperative VA >1 across three treatment groups was carried out with the results as shown in Table 3. In all the three groups, the difference in the proportion of cases with
DISCUSSION

Management problems which are seen in cases of RRD with coexisting MHs are successful anatomical retinal reattachment and closure of MH. In spite of anatomical success attained by various techniques, visual gain is usually poor in this subset. One cause of poor visual gain in these patients is drainage of the fluid through MH which may enlarge the hole and disrupt photoreceptors (PRs) and RPE cells.

MH surgery was first introduced by Kelly and Wendel.[13] Since then, various refinements in the techniques were explored to increase the anatomical and functional success rate in such cases. It was Yooh et al.[14] who showed the role of ILM in the pathogenesis of MH. RD with concomitant MH is not a common entity, but the need of re-operation in such cases is significantly higher compared to RD with no coexisting
Table 1: Comparison of baseline characteristics of patients across three treatment categories (n=23)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Inverted flap (n=7), n (%)</th>
<th>No (n=6), n (%)</th>
<th>Yes (n=10), n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>57.28 (11.31)</td>
<td>60.17 (3.75)</td>
<td>61.70 (7.50)</td>
<td>0.650*</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2 (28.6)</td>
<td>2 (33.3)</td>
<td>4 (40.00)</td>
<td>0.885</td>
</tr>
<tr>
<td>Male</td>
<td>5 (71.4)</td>
<td>4 (66.6)</td>
<td>6 (60.00)</td>
<td></td>
</tr>
<tr>
<td>Preoperative VA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 1 | 1 (14.3) | 1 (16.7) | 5 (50.00) | 0.558  
| 2 | 1 (14.3) | 1 (16.7) | 5 (50.00) | |
| HM | 6 (85.7) | 4 (66.6) | 5 (50.00) | |
| PL | 0 | 1 (16.7) | 0 | 0.312 |
| PL+ | 0 | 0 | 1 (10.00) | |
| Lens status | | | | |
| IOL and aphakic | 7 (100) | 0 | 9 (90.00) | < 0.0001 * |
| Others** | 0 | 6 (100) | 1 (10.00) | |


Table 2: Overall comparison of visual acuity of patients before and after treatment

<table>
<thead>
<tr>
<th>Postoperative VA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA=1</td>
<td>VA&gt;1</td>
</tr>
<tr>
<td>Preoperative VA=1 (n=23)</td>
<td>16</td>
</tr>
<tr>
<td>VA: Visual acuity</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Comparison of visual acuity of non-myopic patients after treatment in three groups

<table>
<thead>
<tr>
<th>ILM Procedure</th>
<th>Postoperative VA, n(%)</th>
<th>Total</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA=1</td>
<td>VA&gt;1</td>
<td></td>
<td></td>
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<tr>
<td>IF</td>
<td>6 (37.5)</td>
<td>1 (14.2)</td>
<td>7</td>
</tr>
<tr>
<td>Yes</td>
<td>7 (46.7)</td>
<td>3 (42.9)</td>
<td>10</td>
</tr>
<tr>
<td>No</td>
<td>3 (18.8)</td>
<td>3 (42.9)</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>7</td>
<td>23</td>
</tr>
</tbody>
</table>


MH as reported by Najafi et al.[1] More chances of failure might be attributed to more chances of PVR in such cases.[1] Studies[1,6,7]

have suggested that addition of SB and use of silicone oil can increase the success rate in cases of RRD with MH with PVR changes. Studies have also shown the importance of ILM.
peel in RRD with MH to increase the success rate.\cite{10} Study by Singh\cite{15} and Shukla et al.\cite{6} showed no difference in anatomical success between groups receiving ILM peel or not. However, as unclosed MH can be a risk factor for re-detachment, inverted ILM flap technique can reduce this risk and need of re-surgery. Meta-analysis\cite{10} showed increased anatomical success rate and more rate of MH closure in cases who underwent inverted ILM peel as compared to ILM peel only in MH-RD.\cite{10} Further, studies\cite{16,17} have shown that MH remained close in recurrent RD cases who underwent inserted ILM tissue during primary repair.

Figure 4: One-month postoperative fundus photograph with silicon oil in situ showing closed macular hole

In our study, all cases were of PVR > C1, ILM peel was done without using PFCL, all cases received silicone oil as a tamponading agent, and none received encirclement band. 50% (3/6) cases had re-detachment in the no peel group, and out of those three cases, two (66.6%) were because of re-opening of MH and one was because of PVR changes in the periphery. In ILM peel group, one recurrence was seen due to PVR changes in the periphery. In our study, no recurrence was seen in the IF group. All the patients had attached retina after re-surgery in cases of re-detachment.

The study by Nazafi et al.\cite{1} reported 50% success rate in no ILM peel group, and similar
are the findings of our study. The study by Shukla et al.\textsuperscript{[6]} had 100% anatomical success rate in their case series even in no peel group. However, their study included cases with PVR grade B only. In addition, in their series, all cases received encirclage band and majority of patients received silicone oil as a tamponading agent even in grade B PVR cases. In our study, one case was post-trauma and two were post-endophthalmitis cases in the no peel group, and out of three cases with recurrent detachment in no peel group, one was post-trauma and one post-endophthalmitis RD. Studies have shown moderate success rate in this subgroup of detachment.\textsuperscript{[18,19]}

Better anatomical success in the IF technique can be attributed to ILM which acts as a scaffold for glial cell proliferation, compensating for retinal shortening,\textsuperscript{[20]} and thereby helps in MH closure and retinal attachment.\textsuperscript{[7,8]}

Various studies have reported variable functional success with different techniques. Although the anatomical success rate has been achieved in nearly 100\% of cases, still the visual gain is not as promising as in other subset of RRD without MHs. In the study by Singh,\textsuperscript{[15]} visual gain was poor in the no peel group compared to the ILM peel group.
However, Shukla et al.\textsuperscript{[6]} reported better visual results in the no peel group. In meta-analysis by Yuan et al.\textsuperscript{[10]} there was no significance in postoperative gain in VA with any of the technique.

The overall visual improvement to LogMar d”1 was seen in 69.5\% of cases in our study. In the present study, 85.7\%, 70\%, and 50\% of the patients achieved final VA of LogMar d”1 in the IF, ILM peel, and no peel group, respectively. The visual gain was seen more in the IF technique compared to no peel, but it was not statistically significant. More amount of vision gain in the IF technique can be attributed to no fluid drainage through MH, thus preventing more iatrogenic damage to photoreceptor cells. Also, inverted flap can cause proliferation of glial cell causing photoreceptors to assume new position in direct proximity to fovea.\textsuperscript{[7]}

Although various modifications in the surgical techniques can achieve attached retina with closed MH in this subset, MH surgery is very demanding in the presence of detached retina. ILM peel can be facilitated with the use of dyes and PFCL, but one should be aware that ILM behaves differently under PFCL. ILM under PFCL has more elastic recoil, and it also eliminates the need of counter pressure to ensure atraumatic peel. Still, peeling an ILM is not free of complications which ranges from trauma to macular PR cells,\textsuperscript{[21]} iatrogenic paramacular breaks, and dye-related photo-toxicity which can have long-term effect on macular function.

**CONCLUSION**

1. Better MH closure and attachment rates can be achieved with inverted ILM flap technique without the use of encirclage band/SB in cases of RRD with concomitant MH with significant PVR changes
2. Visual gain is seen more in inverted ILM peel group compared to no peel group
3. Although challenging and not free of complications, inverted ILM peel can be considered as procedure of choice in these cases.
LIMITATIONS

The study has a small sample group. Large, randomized studies needed to confirm the better results with inverted ILM flap technique in this subset of RRD.

REFERENCES


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