Proceeding of the AIOC 2022
Mumbai
PROCEEDINGS OF AIOC 2022 MUMBAI

Editor

Dr. Arup Chakrabarti

Proceedings of the

80th Annual Conference of

All India Ophthalmological Society
THE NEXT ADVANCEMENT IN PRESBYOPIA CORRECTION.

NEW! AcrySof® IQ PanOptix™
Presbyopia-Correcting IOL

Designed for more natural adaptability

The AcrySof® IQ PanOptix™ IOL features ENLIGHTEN™ (ENhanced LIGHT Enhanced) Optical Technology to mimic the performance of a healthy crystalline lens:
• Exceptionally high light utilisation in a presbyopia-correcting IOL.
  Transmits 98% of light to help provide crisp quality of vision at all distances.1
• More comfortable near to intermediate range of vision.
  Provides a more natural intermediate focal point of 60 cm, which is preferred for real-life tasks, such as computer work, over the 80 cm distance offered by other trifocals.2
• Less dependence on pupil size.
  4.5 mm diffractive zone designed for excellent performance in all lighting conditions.3

To learn more, talk to your Alcon sales representative.

OFFICE BEARERS OF AIOS 2021-2022

President Dr. Lalit Verma
President Elect Dr. Harbansh Lal
Vice President Dr. Samar Basak
Hony. General Secretary Prof. Namrata Sharma
Joint Secretary Dr. Chaitra Jayadev
Hon. Treasurer Prof. Rajesh Sinha
Joint Treasurer Dr. Ajay Aurora
Editor Journal Dr. Santosh G Honavar
Editor Proceedings Dr. Arup Chakrabarti
Chairman Scientific Committee Dr. Partha Biswas
Chairman ARC Dr. Chitra Ramamurthy
Immediate Past President Dr. Barun Kumar Nayak

Members - Scientific Committee

Dr. Partha Biswas, Dr. Krishna Prasad Kudlu, Dr. Somasheila I Murthy, Dr. Amit Porwal, Dr. Jatinder Singh Bhalla, Dr. Parikshit Gogate, Dr. Sonu Goel,
Dr. Fairooz Puthiyapurayil Manjandavida

Members Academic Research Committee
Dr. Rohit Saxena (North Zone), Dr. Shrinivas M. Joshi (South Zone), Dr. Satyajit Sinha (East Zone), Dr. Harshul Tak (Central Zone),
Dr. Anagha Heroor (West Zone)

Editorial Board

Editor: Dr. Arup Chakrabarti
Managing Editor: Dr. Sayan Das, Dr. Jitendra Jethani
Members: Dr. Partha Biswas (Ex-Officio),
Dr. Santosh G. Honavar (Ex-Officio), Dr. Chitra Ramamurty (Ex-Officio),
Dr. Inter Mohan Rustagi (Ex-Officio),
Dr. Narinder Kumar Taneja (Ex-Officio)

All rights reserved. No part of this publication may be reproduced in any form or by any means without prior permission of the editor.

Inquiries or comments may be directed to the editorproceedings@aios.org

Published by Dr. Arup Chakrabarti on behalf of All India Ophthalmological Society. Published at 8A, Karkardooma Institutional Area, Near Deepak Memorial Hospital, Karkardooma,
New Delhi-110092.
Editorial Assistants

Dr. Jeyanthan
Managing Partner and
Chief Consultant,
Paediatric ophthalmology and
Refractive surgery Unit,
of K.S. Eye Hospital and
Aalayam LASIK Laser,
Erode

Dr. Pranav Ranjan
Consultant Eye Surgeon and
HOD
Kurji Holy Family Hospital &
Renu Eye Centre, Patna

Dr. Tanpreet Pal Singh
Consultant
Phaco-Refractive &
Glaucoma Services
Guru Nanak Dev
Netralaya, Jammu

Dr. M. Vanathi
Dr. R.P. Centre for
Ophthalmic Sciences
(AIIMS)
Cornea, Cataract &
Refractive Services

Dr. Arun Kshetrapal
Chief Consultant,
Kshetrapal Eye Hospital and
Lasik Laser Centre, Ajmer

Dr. Sayan Das
Consultant, Cornea,
Cataract and
Refractive Services
Susrut Eye Foundation
and Research Center
Dr. Amarendra Deka
Senior Consultant, Mission Nethralaya, Shillong

Dr. Bijita Deb
A B Superspeciality Eye Hospital, Raipur, Chhattisgarh

Dr. Somasheila Murthy
Head of Service, Corneal Diseases, Tej Kohli Cornea Institute, Consultant, Uvea Service, LVPEI, Hyderabad

Dr. Himadri Choudhury
Vitreoretina Consultant Choudhury Eye Hospital and Research Centre Shyamaprasad Road (Shillongpatty), Silchar,

Dr. Atheek Shaik
Managing partner Fathimah eye hospital Academic director Fathimah eye institute of optometry Managing committee member

Dr. Nazneen Nazm
Assistant Professor Department of Ophthalmology ESI-PGIMSR, ESI Medical College and Hospital
Dr. Manoj Chandra Mathur
Senior Consultant
Glaucoma /
Comprehensive Ophthalmology
Swarup Eye Centre, Medivision
Brij Netralaya: Eye Clinic
Past President TOS & President HOA

Dr. Mita Joshi
Consultant, Shalby Hospital, Indore

Dr. Ganesh V Raman
Chief, Glaucoma Services, Aravind Eye Hospital, Avinashi Road, Coimbatore

Dr. V.P. Gupta
MAMC And NOW, University College Of Medical Sciences, Delhi
1986 Director Professor

Dr. Meena Nair
Senior Consultant Glaucoma Services, Chaithanya Eye Hospital & Research Institute Thiruvananthapuram

Dr. Navin Jayakumar
Honorary Director, Darshan Eye Clinic, Chennai
Dr. Kiran Gopalakrishnan
Consultant in Glaucoma and Anterior Segment, Precise Speciality Eye Care, PMG Junction, Thiruvananthapuram

Dr. C. Senthil Nathan
Chairman and Medical Director, Ramana Eye Centre, Super Specialty Ltd, Lacrimal, Orbit Centre, Chennai

Dr. Subashini Kaliaperumal,
Professor and Head, Dept of Ophthalmology, JIPMER, Puducherry

Dr. Sumita Agarkar
Deputy Director, Pediatric Ophthalmology and adult strabismus service Sankara Nethralya, Chennai

Joint secretary, Strabismus and Pediatric Ophthalmology

Dr. Sandra Chandramouli
Consultant Pediatric Ophthalmologist/ Strabismus at Aravind Eye Hospital, Coimbatore

Dr. Ramesh Babu Bobbili
Medical Director, Academics, Maxvision Super Speciality Eye Hospitals, Visakhapatnam, Andhra Pradesh
Dr. Jitendra Jethani  
Director, Baroda Children Eye Care and Squint Clinic, Vadodara

Dr. Giridhar Bellamkonda  
Superintendent and Head of Department of Ophthalmology, Regional Eye Hospital, Warangal

Dr. Dipankar Das  
Senior Consultant, Department Of Ocular Pathology, Uveitis & Neuro-Ophthalmology Services, Sri Sankaradeva Nethralaya, Guwahati

Dr. Anand Rajendran  
Professor & Head, Vitreo - Retinal Service, Aravind Eye Hospital, Chennai

Dr. Prabu Baskaran  
Vitreo - Retina Surgeon, Aravind Eye Hospital, Chennai

Dr. Apoorva Ayachit  
Consultant Vitreoretina, M M Joshi Eye Institute, Hubblili
CONTENTS

Office Bearers and Other Details

Editorial Assistants

Presidential Address

Editorial Address

Best Free Paper Awardees

Disclaimer
PRESIDENTIAL ADDRESS

Respected Past Presidents, Respected Seniors, Colleagues, & My Dear friends:

At the outset, let me express my heartfelt gratitude to the members of All India Ophthalmic Society (AIOS) for bestowing upon me this honor of leading your society as its President.

I feel greatly honored to be present before you today and welcome you all to the City of Dreams Mumbai.

It's my proud privilege to address the galaxy of Ophthalmologists, my Seniors, Mentors, colleagues, friends, fellow members, students, guest faculties & delegates from different countries.

All India Ophthalmological Society today is a vibrant society, with over 25000 life members, the largest such society of Ophthalmologists in the World. It has its own headquarters in New Delhi. Annual Conference of AIOS is one of the best ophthalmic conferences in the world.

I would like to acknowledge the tremendous contribution made by the
Members, Managing Committee, past presidents, secretaries, treasurers, scientific committees & other wings of the AIOS who have contributed to this stupendous growth of our Society.

Last two years, we all have gone through unprecedented times. Onset of COVID, national level lockdowns, shortage of essential medicines for COVID, Oxygen shortage, non availability of beds in hospitals, stressful duties of health workers it has been tough in many ways. We as AIOS family have also lost some of our beloved members. I express my heartfelt condolences to their families.

I would also like to thank Dr B K Nayak for the lovely introduction. It is a wonderful feeling to see your Picture amongst the Legends who have led AIOS in the past. I am truly humbled.

I would also like to thank Local Organizing Committee of Dreamcon AIOC 2022 led by Dr. T P Lahane, Dr. B K Nayak, Dr. Quresh Maskati, Dr, Parikshit Gogate, Dr. Prashant Bawankule & Dr. Ragini Parekh (President BOA ) for making wonderful arrangements to make AIOC 2022 a memorable event for all of us.

Advocacy Team

As you know, I have been closely associated with AIOS for 23 years in different capacities. Often in the past, Presidents have given great suggestions for betterment of society & set ambitious goals regarding prevention of blindness, diabetic retinopathy, childhood myopia,… etc.

However it is often not possible to fulfill those goals as the term of
president is only for one year. Such goals need long term planning and close coordination with union government, state governments, local administration, civil society, hospitals etc.

**Therefore I propose** to setup an advocacy team which will work in close coordination with Government & all other stakeholders and ensure AIOS as National Society of Ophthalmologists in India has a key role in formulation of National Programme, Policies, National Surveys, TPAs, Rates of procedures / Surgeries etc.

For me, Interest of AIOS, Interest of Members is & shall be of paramount importance & We shall gear all our activities accordingly & The RED BOOK of AIOS (Memorandum, Rule & Regulations & Byelaws) is our Bible & shall be guiding all our activities.

What am I going to talk is How can I work with your Cooperation to benefit the members to benefit the AIOS I have been into AIOS for over 2 decades & during these years Have worked With Single Aim ”Upliftment of AIOS & its members” Whether it is Head Quarters Whether it is Finance Whether it is Membership Whether it is Scientific Program All these would not have been possible. But for the Support of Governing Council & ALL of You NOW, Let me dwell on couple of things, which I propose to be pursuing in the coming year:

**Mid Term Conference**

As of now, our Annual AIOS conferences are held in bigger cities which have adequate infrastructure for 7000-8000 delegates, associated
accommodation facilities & rail/road/air connectivity from different parts of the country as well as International.

To facilitate our members from smaller towns & remote areas of the country, to participate in scientific deliberations & update & upskill themselves with advances in Ophthalmology, I propose to hold Mid term AIOS conferences in Tier 2 / Tier 3 cities.

This has been pending for sometime. & we plan to take this forward with your valuable support.

**Skill Transfer Facilities at AIOS Headquarters**

We all know & understand that Ophthalmology is primarily a surgical specialty. Theoretical knowledge you can gain by attending various conferences or through various online channels.

BUT to develop Surgical Skills / Diagnostic skills, One needs to learn them from the Masters .... One needs to practice on experimental eyes ... One needs to work on Simulators ..... 

One needs a guiding hand ..... 

This was the whole inspiration & thought process behind organizing SSTC (Surgical Skill Transfer Course) , DSTC (Diagnostic Skill Transfer Course) & TSTC (Technology Skill Transfer Course) courses during Annual Conference of AIOS with the support of our trade Partners.

Encouraged by overwhelming response to these courses , we propose to establish facility for Skill Transfer Courses at AIOS HQ . AIOS Secretariat
will enroll desirous members and will also rope in the experts / mentors in respective fields and workout a schedule for such courses throughout the year.

**AIOS headquarters & its Wings**

All the wings of AIOS viz. Secretariat, Scientific Committee, ARC, Editor, Proceedings & Editor IJO are doing great job, individually.

I propose to give each wing enough freedom to enable/empower them to pursue the objectives of their respective domains .. BUT after having it discussed & passed in GC & within the framework of our rule book & within the resources allocated to them & Always Keeping the interest of members in the forefront.

I would wish that all 5 wings work in harmony and cohesion like 5 fingers of a fist.

You see fist always has more power than individual fingers.

**International Recognition of AIOS**

Today AIOS is the second largest body of Eye Surgeons in the World & Largest body of Life Members in the World.

However, Despite the numbers, Despite Huge Talent , We somehow have not been able to project AIOS as a body to reckon with internationally.

Individually many of our members are very well known all over the world & we are proud of them. AIOS as a body, is however yet to get its due recognition. Efforts have been made in the past to project AIOS
internationally.

I plan to pursue this mission with full force and make AIOS a global name & AIOS annual conference the most sought after Ophthalmological Conference in the World. I urge your participation & cooperation to pursue this ambitious goal.

**FAICO**

With help of Dr Azad & Dr Babu Rajendran, we conceptualized the much popular FAICO .. the Fellowship of All India Collegium of Ophthalmology. Launched in 2009 and implemented in 2010, FAICO received tremendous response from members.

FAICO, the one of its kind in the World, is an innovative concept & much needed in ophthalmology with so many super specialties.

We should try to make FAICO globally recognized. FAICO needs to be projected in SAARC region, Asia Pacific, Africa & subsequently the entire World.

**Managing Committee Members & State Societies**

We have with us – State level societies, which are affiliated with AIOS & most of them have two of their representatives as AIOS Managing Committee members. All of these members are distinguished ophthalmologists and are doing great job in their respective states. However there is hardly any active involvement of Managing Committee in functioning of AIOS, towards its vision & mission.
Couple of years ago – MC meeting used to be held only once & that too during Annual conference. When I was Secretary of your society, I had introduced the system of Mid term meeting of Managing Committee, with an objective to improve Centre-State connect”.

I propose to take this relationship further and leverage the strength of our State Societies towards fulfillment of AIOS mission.

All affiliated state societies will be encouraged to promote scientific & educational activities. Based on the work done by all states, Best state will be honored with President`s Medal during Annual Conference.

We will convene a day long workshop with MC members to prepare a framework & objective criterion for selection of best state society.

For this, I plan to involve MC members of affiliated states, & also utilize the services of Joint secretary & Joint Treasurer of our AIOS body.

Public Awareness

Various wings of AIOS have been doing a great job in dissemination of scientific knowledge on various aspects of eye care on a regular basis through conference, webinars, proceedings, journal & CME series, for the benefit of its members.

I feel, its equally important to create awareness about common eye diseases & their symptoms amongst the public at large. While some efforts have being made in this direction, we need to do much more. Such an awareness about common eye diseases among masses will help in early
detection of disease, its treatment, leading to prevention/reduction of blindness.

I propose to launch a series of Public Lectures by eminent Ophthalmologists on a regular basis.

It would be wonderful if we could make efforts to make these lectures available in different languages so that more and more people are befitted across the country.

Before I close, I would like to express my heartfelt gratitude to my Family (My parents, Wife Neeta, & children: Nitin, Neha & Aastha).

Gratitude to my Extended Family (Centre for Sight – Dr Mahipal, Dr Alka & entire CFS Family & RPC Colleagues) who stood rock solid with me & also helped me Professionally, Financially & Socially & made it possible for me to Stand before You Today.

I am also indebted to lots of Friends, Colleagues and Trade partners for their valuable support.

I would also like to thank my friends in AIOS: Dr. Barun Nayak, Dr. Harbansh Lal, Dr. Mahipal Sachdev, Dr. Namrata Sharma, Dr. Rajesh Sinha, Dr. Partha Biswas, Dr. Chitra Ramamurthy, Dr. Santosh Hanovar, Dr. Arup Chakrabarti for their tremendous contribution & look forward to their continued support.

I also commend contributions of Mr. Kripal & the entire AIOS staff for their unstinted support.
I wish AIOC 2022 Conference a great Success and I am sure with the kind of hard work put in by our Local Organizing Committee, power packed content by Scientific Committee, state of art show by our Trade Partners & efforts of all wings of AIOS, this world class venue, AIOC 2022 will be a memorable event.

I know I have put in an ambitious Plan for next year.

But I am confident, together we can achieve all of this. You will agree, in all these, interest of members of AIOS is at the centre.

I therefore once again urge all of you for your valuable contributions & whole hearted support to make this happen.

Together We Win..

Long Live

AIOS Jai Hind

Dr Lalit Verma

President, AIOS
EDITORIAL ADDRESS

Editor Proceedings Report - AIOC 2022, Dr. Arup Chakrabarti

Dear Esteemed Colleagues


I am grateful to have received an opportunity to serve you through AIOS (for 2 consecutive terms) and be instrumental in ushering in epochal changes in the way scientific contents are archived, managed and disseminated for the common benefit.

As you may already be aware, most of the scientific contents of the AIOS annual meetings (2017 to 2022) are available to AIOS members (free of cost) at a searchable (key words) and very easy to navigate http://proceedings.aios.org/.

You can access the curated contents and presentations herein on-the-go regardless of your geographical location. You only need a reasonable Wi-Fi/data connection and your Smartphone or tablet device.
**AIOS On Demand** has truly been a game changer in the way knowledge is shared and esteemed colleagues across the spectrum (be it a resident preparing for a seminar or a teacher preparing to deliver a podium lecture) have been extremely appreciative of this initiative.

**AIOS Activities for the Year 2022**

We witnessed 2 major AIOS meetings this year – the usual annual meeting in Mumbai and the Mid-term meeting in Patna. As a result, we had an opportunity to cover a wider spectrum of scientific work. We were extremely glad to take on this challenging responsibility.

As you are aware 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 AIOS meetings. In addition to what was already on the platter in 2022 we also started sending 2 additional weekly mails to cover the mid-term meeting to 26,000 plus AIOS members the opening rate of which has been extremely high. This means our team dispatches 4 well curated emails on popular topics on a weekly basis. This has necessitated proper planning throughout the year and I would like to thank the personnel connected with developing, processing and managing the contents from the bottom of my heart.

**Proceedings website:**

The annual AIOC 2022 was an in-person meeting this year and the Team
scientific committee had done a very good job - it was an academic feast. As the Chairman Scientific Committee had mentioned about 402 programs were running in all the halls. Like in 2021, these programs were actually not planned to stream live in any other channel in accordance with the OBSC decision. Team EP had been receiving links and downloading data 24 x 7 for all the scientific presentations on a daily basis from the AV team engaged by the AIOS secretariat. Due to sheer volume of the data this activity stretched out to about a week or so after the conference. The downloaded contents were processed and rendered suitable for utilization. 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. Incidentally like in the years before the email campaign started immediately after the 2022 conference without any lag and is continuing till date.

If you visit the website (http://proceedings.aios.org/) you will find abstracts of all the submitted sessions. The proofread texts (to whatever extent it was possible taking into account the quality of submission) of the best paper of the sessions (BPOS) have also been uploaded in a pdf format on the website. I want to thank the proof-readers (who have been gratefully acknowledged) for taking their time out and go through this humongous task of proof reading the submitted texts. I had already registered a request with the GC to do away with the FP texts the (quality
of which leaves a lot to be desired) since these are of no consequence as regards the BPOS selection. In a few cases of BPOS there has been no accompanying text. In compliance with the OBSC decision taken in 2020 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 was going through during the COVID days.

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 26000 plus AIOS members are also archived in the communication page of the website. We received about 24 TB of data after the 2022 conference and though it was quite humongous amount of data - it was crunched and ultimately, uploaded on the YouTube channels of the editor proceedings.

Request to the AIOS president and secretariate to involve the Editor Proceedings in the discussions while finalizing the AV vendor has been made on an annual basis. For the year 2023 vendor selection and negotiations have been conducted solely by the OBSC and the Team EP sincerely hopes that the carefully laid down AV guidelines for optimal performance have been adhered to. This will go a long way in preventing the recurring recording mistakes that have plague the AV activities year after year. 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 continued with the mass email campaign initiated by Team EP right from the beginning of the first term for the last couple of years. This year so far, we have sent out about 89 mass emails to more than 26000 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 294763 email reads have been noted.

**Activities for the AIOC 2023**

I would like to thank the outgoing President Dr. Lalit Verma for his wonderful tenure and complete support in my endeavours. He has been responsible for raising the bar for all facets of AIOS activities. I would like to welcome our incoming President Dr. Harbans Lal 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.

As my term as EP draws to a close, I derive tremendous satisfaction in
having been able to serve you and it brings treasured memories as I look back.

New team will take over and along with the advent of newer technologies I am sure this platform will become even more relevant to you.

I am happy to have been part of your journey.

Wrapping up while wishing you the very best in all your endeavours

I remain

Yours Sincerely

Dr. Arup Chakrabarti

arupeye@gmail.com

editorproceedings@aios.org
Best Free Paper Awardees

AIOS – Sante Vision Award (Cataract) - Dr. Nikhil Balakrishnan (B20247) - Paper [Fp955] : "Baseball Bat“ Sign:-Predicting Prevalence Of Intraop Floppy Iris Syndrome In Patients On Tamsulosin

AIOS - J.S. Mahashabde Award (Community / Social Ophthalmology) - Dr. Maheshwari S (M20021) - Paper [Fp1637] : Trash To Treasure Retcam-Treasure To Save Sight Amidst Pandemic

AIOS – Apos K. Vengala Rao Award (Comprehensive Ophthalmology) - Dr. Haimanti Choudhury (C10327) - Paper [Fp2323] : Novel Artificial Intelligence (Ai) Derived Dry Eye Analyzer – Is It Here To Stay?

AIOS - Cornea Award - Dr. Rakhi Kusumesh (K11392) - Bihar Ophthalmological Society : Miltefosine Related Keratitis: Clinical Characteristics And Management

AIOS – Rema Mohan Award (Diabetic Retinopathy / Medical Retina) - Dr. Siddharth Narendran (S16890) - Paper [Fp442] : Mechanotransduction: A Paradigm Shift In The Pathogenesis Of Age-Related Macular Degeneration
AIOS - Apos-Pradeep Swarup Award (External Disease) - Dr. (Mrs.) Kasturi Bhattacharjee (B07299) - Paper [Fp668] : Platelet Rich Fibrin As 3-Dimensional Structural Scaffold In Surface Wound Healing Of Eye And Orbit

AIOS – D B Chandra Disha Award (Glaucoma) - Dr. Prithvi Chandrakanth (C22539) - Paper [Fp1704] : Smartphone Gonio-Imaging

AIOS – Apos Santhosh Honavar Award (Lacrimal) - Dr. Pragya Saini (P20087) - Paper [Fp2287] : Update On The Long-Term Outcomes Following The Management Of Incomplete Punctal Canalization

AIOS – S D Athawale Award (Neuro Ophthalmology) - Dr. Swati Phuljhele (P10477) - Paper [Fp877] : Evaluation Of Oct – Angiography Changes In Non-Arteritic Anterior Ischemic Optic Neuropathy

AIOS - Ocular Pathology / Ocular Oncology And Tumors Award - Dr. Swathi Kaliki (K13050) - Paper [Fp441] : Artificial Intelligence And Machine Learning In Ocular Oncology: Retinoblastoma

AIOS - Optics/ Refraction / Contact Lens - Dr. Pallavi Joshi (J14456) - Paper [Fp1580] : Learning Curve In The Construct Of Smartphone-Based Keratoscope Prototype For Kcn Screening
Aios – Sujatha Savitri Rao Award (Orbit / Oculoplasty) - Dr. Rolika Bansal (R21494) - Paper [Fp1614] : Local Tumor Control By Adjuvant Plaque Brachytherapy In Conjunctival Melanoma

AIOS – Hanumantha Reddy Award (Pediatric Ophthalmology) - Dr. Sonali Rao (R15501) - Paper [Fp1838] : Impact Of Screen Time On Ocular Surface In Children

AIOS – Shiv Prasad Hardia Award (Refractive) - Dr. Sharon Dsouza (D13923) - Paper [Fp1553] : Effect Of Cap Depth In Smile On Clinical, Biomechanical And Molecular Outcomes

AIOS – Prem Prakash Disha Award (Squint) - Dr Neena R (M12228) - Paper [Fp440] : Acute Acquired Comitant Esotropia Precipitated By Excess Near Work During Covid-19 Home Confinement

AIOS – Rakesh Sharma Memorial Award (Trauma) - Dr. Mehul Shah (S05624) - Paper [Fp1991] : Toddlers Ocular Trauma Score A New Predictive Model For Children With Ocular Trauma
AIOS – Narsing A Rao Award (Uvea) - Dr. Manisha Agarwal (A07736) - Paper [Fp993] : Correlating The Vegf Levels With The Prompt Clinical Regression Of Tubercular Granulomas

AIOS – S Natarajan Award (Vitreo - Retina) - Dr. Subhadra Jalali (S014027) - Paper [Fp614] : Short Term Outcomes Of Combined Buckle And Scleral Imbrication For Complex Retinal Detachments
BEST FREE PAPERS
DISCLAIMER

Neither Editor – AIOS Proceedings, nor any other party involved in the preparation of materials contained in the proceedings of AIOC 2022 assumes any liability or responsibility for the accuracy, completeness or usefulness of any information published in the proceedings. We are not responsible for any errors or omissions or for the results obtained from the use of such material. The entire responsibility of data integrity and quality of the published manuscript rests with the respective authors.
CONCEPT PAPER ON USING 3D MODELLING TO LEARN SURGERIES

Introduction:

Covid pandemic has brought many new things, of which disruption of physical learning in medicine world pained all the trainee doctors. [1] Newer problems ask for innovative solutions. Computer simulations has always been a part of training modules of different instruments. Question that hovered around is application of software into learning and skill enhancement. Conventional modelling was difficult to reproduce as most of them were copyrighted, and difficult to procure. There is past experience, although mostly in the sphere of anatomical reproduction, orbital anatomy, dynamic modelling for developmental studies or congenital malformations [2].

We tried is to produce a basic model of cornea with intricate details, reproduced as far as we can. Tissue properties have been incorporated as best as possible. We tried to initiate the concept of model learning as a part of information revolution.

Materials and methods:
Licensed version of 3D modelling was used to create a corneal model with all the layers, and their possible variations (limited although).

These models are easily sharable and can be seen over a range of digital devices.

It was circulated among randomized number of ophthalmologists, both trainee and seniors (with specialization in ophthalmology and at least 3 years of experience).

The models were magnifiable, and with cross sections as far as possible.

Post 10 hours of use of these models, multiple response model method was used to score the post use learning of the 13 users.

Responses were analyzed on regression analysis.

**Results:**

Users reported better acceptance, better representative ability, better simulation, easy availability over phone and improved sharing capacity. (Cumulative frequency model on regression analysis).

P value for acceptance was 0.04 while better simulation was 0.03, availability was 0.02 but others individually were non-significant. Taken together, factors were found to be significant.

**Discussion:**

3D modelling or computer modelling can be an excellent complement to conventional method of learning. Easy use and availability across platforms can be its turnaround point. Understanding of diseases and their natural history can be better replicated.
Conclusion:

Three-dimensional modelling can be an alternative way of learning although it requires lot of development and studies to prove its efficacy.

Bibliography


"BASEBALL BAT" SIGN : PREDICTING PREVALENCE OF INTRAOPERATIVE FLOPPY IRIS SYNDROME IN PATIENTS ON TAMSULOSIN

Abstract

Purpose:

To study the prevalence of Intraoperative Floppy Iris Syndrome (IFIS) in patients on Tamsulosin using the “Baseball Bat” sign using Anterior Segment OCT (AS-OCT)

Methods:

This case control study was carried out at a single center over a period of 3 years. Patients were divided into 2 groups. Group A included 76 eyes on Tamsulosin and Group B included 76 eyes not on tamsulosin. All the patients from both the groups scheduled for Cataract Surgery underwent preoperative AS-OCT. Iris pattern of these patients were studies & clinically correlated it with the occurrence of IFIS.
Significant thinning of the Dilatory Muscle Region (DMR) of the iris was noted, giving it a resemblance akin to a “Baseball Bat”. 85.52% (56 of 76) of these patients demonstrated a positive sign. 96.05% (73 of 76) of patients with a positive sign showed signs of IFIS, denoting a strong correlation (p<0.05%). None of the 8 patients with negative sign showed characteristics of IFIS.

Conclusion:

“Baseball Bat” sign can be effectively used as a marker to predict IFIS in patients on Tamsulosin & intraoperative measures can be taken to prevent the same.

INTRODUCTION

Intraocular floppy iris syndrome (IFIS) is a known complication of phacoemulsification cataract surgery. Chang and Campbell first published their epoch-making article on what they named intraoperative floppy-iris syndrome (IFIS).¹ It consists of the classic triad of intraoperative miosis, billowing of the iris, and prolapse of iris tissue through corneal paracenteses.² IFIS has been reported in 2–9% of surgeries²-⁵, and is related to numerous other intraoperative and postoperative complications including rupture of the posterior capsule, vitreous loss, nuclear prolapse, iridodialysis, iris defects, postoperative elevation of intraocular pressure (IOP), and endophthalmitis.³-⁶

The most recognized risk factor for IFIS is current or previous exposure to alpha-antagonists.³-⁸ Tamsulosin (marketed as Flomax), is a selective α-1A adrenergic blocker used for the treatment of benign prostatic
hypertrophy (BPH) and hypertension by relaxing smooth muscle. Other risk factors for IFIS include hypertension$^{4,7}$, male gender$^{5-8}$, older age$^5$, smaller mydriatic pupil diameter, and inconsistently short axial length$^{8-11}$.

$\alpha$-1adrenergic receptors are also present on the dilator muscle of the iris. Hence, patients on $\alpha$-1adrenergic antagonists (Tamsulosin) may suffer from IFIS. Therefore, the aim of the study was to predict the occurrence of IFIS in patients of Tamsulosin.

**MATERIALS AND METHODS**

**i) Study Design and Participants**

This case control study was strictly adherent to the tenets of the Declaration of Helsinki, and was undertaken following ethics committee approval of our hospital. Informed consent was obtained from each patient undergoing the surgery. Patients were divided into 2 groups. Group A included 76 cases on tamsulosin > 3 months and Group B included 76 controls not on tamsulosin. All the patients underwent the cataract surgery at Sai Deep Eye Clinic, Mumbai during a period of 3 years (January 2019-January 2022).

**ii) Inclusion and Exclusion Criteria**

Male patients above the age of 55 years with cataract were included in the study. Patients using drugs other than Tamsulosin for BPH, glaucomatous patients on anti-glaucoma medications, complicated cataracts and any condition that could alter the iris morphology like diabetes mellitus were excluded from the study.

**iii) Examinations**
All the patients underwent the routine preoperative cataract assessment along with infrared pupillometry and undilated Anterior Segment Optical Coherence Tomography (AS OCT). Both photopic and scotopic pupil size were measured at 40 lux and 0.04 lux, respectively using the wave light corneal topolyzer. Undilated ASOCT was done to assess the iris structure and pattern.

iv) Data Analysis

All the data sets were maintained and managed on an Excel Spreadsheet. The MedCalc ® Statistical Software Version 18.11.6 (MedCalc Inc, Ostend, Belgium) was used for data analysis. A p-value less than 0.05 was considered to be statistically significant.

RESULTS

The mean age was 62.4 ± 7.3 years in Group A and 61.9 ± 8.4 years in Group B with no statistical significance among the two groups. The Dilator Muscle Region Thickness (DMRT) was reduced to a mean of 382.4 ± 78.3 mm in the test group. The mean DMRT in the control group was 507.8 ± 78.4 mm [FIGURE 1]. The difference in the mean DMRT between the two groups was statistically significant (p<0.017) [Table 1]. However, there was no statistical significance noted in the Sphincter Muscle Region Thickness (SMRT) between the two groups (p=0.10). The ratio of the DMRT/SMRT was reduced to a mean of 0.75 ± 0.13 in Group A when compared to 0.98 ± 0.17 of Group B. The reduction in the ratio of DMRT/SMRT between the two groups was statistically significant (p<0.034).

The mean photopic pupil size in group A and the group B was 2.76 ± 0.48
and 3.59 ± 0.42, respectively. The reduction in the photopic pupil size in group A was statistically significant (p<0.001). Similar, reduction in the scotopic pupil size was noted in group A and was statistically significant (p<0.001) [Table 2]. However, the ratio between the photopic and scotopic pupil size was not statistically significant between the two groups (p=0.078). Patients from both the groups underwent phacoemulsification cataract surgery under peribulbar anaesthesia (2.8 mm temporal corneal incision). During the cataract surgery, none of the patients developed signs of IFIS in group B. However, 62 out of 76 eyes developed 1 of the 3 signs of IFIS in group A [TABLE 3].

DISCUSSION

We report a novel technique to predict the occurrence of IFIS by using ASOCT. It is the first study to demonstrate the thinning of Iris DMR Thickness in patients on Tamsulosin. This thinning of DMR resembles a baseball bat on ASOCT and hence this sign on ASOCT is coined as “Baseball Bat Sign” [FIGURE 2]. This study also demonstrates that there is inadequate pupillary dilatation in patients on tamsulosin using infrared pupillometry on wave light corneal topolyzer. Due to the presence of this sign on ASOCT, we are better prepared to tackle IFIS. Multiple steps are taken to avoid the signs of IFIS intra-operatively. These includes creation of longer wounds, controlled hydro-dissection, avoid overfilling the anterior chamber with viscoelastic, decompressing the anterior chamber periodically and using a low flow phacoemulsification setting.
DISCLOSURE

The authors report no conflicts of interest in this work.
### Table 1: Iris Measurements

<table>
<thead>
<tr>
<th></th>
<th>TEST GROUP</th>
<th>CONTROL GROUP</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilator Muscle Region Thickness (DMRT)</td>
<td>382.4 ± 78.3</td>
<td>507.8 ± 78.4</td>
<td>p&lt;0.017 Significant</td>
</tr>
<tr>
<td>Sphincter Muscle Region Thickness (SMRT)</td>
<td>506.4 ± 87.3</td>
<td>518.9 ± 83.4</td>
<td>p=0.10 Not Significant</td>
</tr>
<tr>
<td>DMRT/SMRT</td>
<td>0.75 ± 0.13</td>
<td>0.98 ± 0.17</td>
<td>p&lt;0.034 Significant</td>
</tr>
</tbody>
</table>

### Table 2: Pupil Measurements

<table>
<thead>
<tr>
<th></th>
<th>TEST GROUP</th>
<th>CONTROL GROUP</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photopic Pupil size</td>
<td>2.76 ± 0.48</td>
<td>3.59 ± 0.42</td>
<td>p&lt;0.001 Significant</td>
</tr>
<tr>
<td>Scotopic Pupil size</td>
<td>5.63 ± 0.57</td>
<td>6.53 ± 0.63</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

42
Photopic Pupil size / Scotopic Pupil size   |  0.49 ± 0.13 |  0.54 ± 0.17 | p=0.078 
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant</td>
<td>Not Significant</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Percentage of Signs of IFIS Seen In Group A Patients

<table>
<thead>
<tr>
<th>FLOPPY IRIS</th>
<th>IRIS PROLAPSING INTO WOUNDS</th>
<th>INTRAOP PUPILLARY CONSTRICTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>48/76 (63%)</td>
<td>28/76 (36.9%)</td>
<td>57/76 (75%)</td>
</tr>
</tbody>
</table>

Figure 1: Normal Iris DMR Thickness in Control Patient
Figure 2: Decreased Iris DMR Thickness in IFIS Patient Giving It A Striking “Baseball Bat Sign” Appearance

REFERENCES


11. Terauchi Y, Horiguchi H, Shiba T (2018) The pharmacological mydriatic pupil-to-limbal diameter ratio as an intuitive predictor for the risk of
NOVEL CM T FLEX LENS IN COMPARISON WITH STANDARD SCLERAL FIXATED LENS AND IRIS CLAW LENS

Abstract

Aim:

To compare the visual outcomes, refractive outcomes and complication rates of the novel CM T Flex IOL (CT) for surgical aphakia with standard Scleral Fixated IOL (SF) and Iris Claw IOL (IC).

Methods:

Prospective non randomised study was done simultaneously at two tertiary eye hospitals. 112 surgical aphakia eyes from Jan to Mar 2019 were included. 73 eyes completed 6 month follow-up (24 had SF, 26 had IC & 23 had CT).

Results:

In 3 groups, there was no difference in basic parameters. Time to secondary surgery was lesser and duration of surgery was shorter in IC (p<0.01).
hypermetropic refraction was seen and AC reaction, irregular pupil and lens tilt were more in IC eyes (p<0.05). At 6m, haptic exposure was seen in 2 SF eyes(p<0.05).

Conclusion:

CT is comparable to SF & IC in relation to refractive outcomes and visual acuity. CT haptic exposure is lesser than SF. Intraocular inflammation and pupil shape wise, CT is comparable to SF and better than IC lens.

Introduction

Ophthalmologists performing cataract surgery are often confronted with complications and placement of an intraocular lenses (IOL) in these eyes with compromised capsular support is a challenge.¹ Scleral fixated IOL (SFIOL) are so designed that the haptics have provisions for suturing or tucking into the sclera for additional stability.² In order to avoid haptic manipulation extra-ocularly, the innovative CM-T Flex IOL was developed. The special T shaped haptics allows for a simple pull and release technique that is sufficient to anchor the haptics to the sclera without the need for additional procedures.³,⁴ This pilot study aims to compare the results of CM T Flex with standard options of 3 piece sutureless SFIOL and iris claw IOL (ICL)

Materials and Methods

The study was retrospective and done by analysing the records of patients who underwent SFIOL, ICL or CM T Flex IOL at two tertiary care institutions in Tamilnadu from January to March 2019. 112 eyes were enrolled. 39 eyes
did not complete a 6 month follow up and were excluded. Finally, 73 eyes (24 SFIOL, 26 ICL and 23 CM T Flex IOL) were studied. Baseline parameters were collected and follow up parameters at 1 and 6 months were reviewed. SFIOL and ICL surgeries were performed by standard techniques. CM T Flex design and surgical technique is elaborated.

**The design of CM-T Flex IOL**

CM-T Flex IOL has a total length of 13.50 mm. It is a hydrophilic foldable lens. An A constant of 118 is used. The refractive index of the material is 1.460. The IOL has a T shaped haptic that is connected to the 6 mm circular optic by means of semi-circular connecting arms. A 10° angulation between the optic and semicircular arms of the haptic prevents iris-IOL touch.

**Surgical technique**

The CM T Flex is introduced into the eye through corneal incision using a cartridge-injector system. The haptic that first enters the eye is guided behind the iris as it is injected. Once behind the iris plane, it is held at the centre of the T shaped haptic with the PraNiv T Flex intraocular forceps (Appasamy Associates, Pondicherry, India) which is introduced into the eye through the sclerotomy under the scleral flap on the left of the surgeon. This is a unique forceps with shorter teeth that prevents cutting of the soft hydrophilic lens. The PraNiv forceps is brought out of the eye thereby exteriorizing the leading haptic. Since the material is hydrophilic, the haptic is bendable and passes through the sclera easily. Once outside, it quickly springs back to its natural shape and anchors itself to the sclera. The trailing haptic, meanwhile, rests on the iris after exiting the injector. Using a side
port, the Nishi grasping forceps (Appasamy Associates, Pondicherry, India) is used to exteriorize the trailing haptic using the handshake technique through the other sclerotomy under the scleral bed at 9’o’ clock meridian. As before, once exteriorized, the haptic immediately opens out and anchors itself to the sclera stabilizing the IOL. At conclusion, the posterior segment is rechecked. The partial thickness scleral flaps were closed with 7-0 vicryl sutures and the regular 3-port 23 gauge sclerotomies are self sealed.

**Statistical Analysis**

All analysis were performed with SPSS version 16 for Macintosh. Demographic and surgical data were tabulated for all three groups. Categorical and continuous data were assessed separately and significance was assumed when P was less than 0.05.

**Results**

The baseline demographic parameters are shown in Table 1. As noted, age, gender, axial length and IOL power were comparable. There was significantly lesser delay in performing ICL surgery when compared to the other two IOLs (P<0.05). Similarly, there was significantly lesser incidence of retained lens material in eyes that underwent ICL implantation (P<0.001). The surgical and post operative outcomes are shown in Table 2 where we noted that duration of surgery is significantly lesser in ICL eyes (P<0.01). One patient with SFIOL required resurgery to reposition the IOL within a month. We also noted a hyperopic postoperative refraction in ICL patients (P<0.05) both at 1 month and at 6 months. There was no difference in visual acuity between the 3 groups.
When analysing post operative complications, all lenses were same with respect to corneal edema, IOL dislocation, vitreous haze and retinal breaks. Anterior chamber reaction, irregularity of pupil and IOL tilt were significantly more in eyes with ICL. Haptic exposure was seen in 2 SFIOls eyes.

Discussion

Different IOLs help clinicians in management of surgical aphakia.\textsuperscript{5,6} Amongst the various options, surgeons prefer the SFIOls. Gabor Scharioth was the one who innovated and popularized the technique of suture less fixation by tucking haptics into the sclera.\textsuperscript{7} Later, Agarwal and colleagues introduced a flap and glue technique to enhance the stability.\textsuperscript{8} The Yamane technique is a recent addition to the surgeons armamentarium where the haptics are flanged and pushed back to rest intra-sclerally.\textsuperscript{9}

Each of the above mentioned methods have use in different scenarios. Many surgeons have adopted one or more of these techniques and have achieved success with them. The common denominator that connects all these techniques is the use of a 3 piece IOL that has prolene haptics. The haptics have to be carefully handled and manipulated gently to achieve the desired final anatomic position to poide for IOL stability. That requires finess and mastery, which comes only with years of experience. A slight misjudgment on the surgeon’s part can lead to haptic bending and breakage, which then necessitates redoing the entire surgery. The learning curve is quite steep with increased surgical time as a result of complex maneuvers.

The CM-T Flex IOL specifically addresses these concerns.\textsuperscript{3,4} It makes haptic
handling easier. Stability of the IOL is not dependent on complex manoeuvres after haptic exteriorization. Instead, this IOL provides for a simple grasp, pull and release technique which simplifies the complexities involved in SFIOL surgery. The IOL has a U shaped haptic design that allows for use in eyes of varying white to white diameters. The hydrophilic design helps in easy maneuvering and offers more pliability when passing through the sclera.

A few results brought out by our study are already known. For example, we noted that visual acuity is comparable between SFIOL and ICL. ICL surgery takes lesser time and that pupil distortion is more and inflammation could also be more in ICL surgery. The novel results that our pilot study provided is that, when compared to SFIOL and iris claw, the novel CM T flex also provides good vision and refractive outcomes.

More importantly, complication profile of the CM T Flex IOL is not high. It is comparable to the standard options. There was no haptic exposure or IOL dislocation. In CM T Flex IOL placement, pupillary shape was maintained with no retinal tears or detachment.

To conclude, the unique design of CM-T Flex IOL helps to simplify the complex procedure of fixing an IOL to the sclera by use of sutures or varied haptic manipulation techniques. Long term follow-up has shown no IOL related complications like inflammation, IOP changes or macular edema. IOL exposure or tilt was also absent.

References


Table 1. Demographic and baseline parameters of participants in the three groups

<table>
<thead>
<tr>
<th></th>
<th>Scleral Fixated IOL (N=24)</th>
<th>Iris Claw IOL (N=26)</th>
<th>CM-T Flex IOL (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, in years, mean</td>
<td>62.3 (51-73; 3.4)</td>
<td>61.4 (49-71; 4.2)</td>
<td>64.2 (54-76; 4.3)</td>
</tr>
<tr>
<td>(range; SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males, N (%)</td>
<td>16 (67)</td>
<td>16 (62)</td>
<td>17 (74)</td>
</tr>
<tr>
<td>Right eye, N (%)</td>
<td>14 (58)</td>
<td>12 (47)</td>
<td>14 (60)</td>
</tr>
<tr>
<td>Axial length, in mm, mean</td>
<td>23.18 (21.43-25.42; 1.24)</td>
<td>22.24 (20.11-26.86; 1.37)</td>
<td>22.98 (19.87-27.56; 1.12)</td>
</tr>
<tr>
<td>(range; SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IOL power, in diopters,</td>
<td>19.45 (17.00-25.5; 2.86)</td>
<td>18.77 (16.50-25.5; 2.55)</td>
<td>20.14 (17.50-24.5; 2.55)</td>
</tr>
<tr>
<td>mean (range; SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IOL delay, in days, mean</td>
<td>3.2 (2-7; 1.3)</td>
<td>1.5 (0-8; 2.6)**</td>
<td>3.4 (3-10; 3.6)</td>
</tr>
<tr>
<td>(range; SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenticular remnants and</td>
<td>21 (87)</td>
<td>4 (14)**</td>
<td>18 (80)</td>
</tr>
<tr>
<td>PPV, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Surgical and followup parameters of participants in the three groups

<table>
<thead>
<tr>
<th></th>
<th>Scleral Fixated IOL (N=24)</th>
<th>Iris Claw IOL (N=26)</th>
<th>CM-T Flex IOL (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of surgery,</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in minutes (range; SD)</td>
<td>40.32 (25-55; 2.45)</td>
<td>12.67 (5 – 25; 1.53)**</td>
<td>25.23 (15 – 35; 2.21)</td>
</tr>
<tr>
<td><strong>IOP at 1 week,</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in mm Hg (range; SD)</td>
<td>12.4 (8-22; 1.45)</td>
<td>11.3 (7-52; 2.41)</td>
<td>12.6 (8-27; 2.16)</td>
</tr>
<tr>
<td><strong>Resurgery within 1 month,</strong> N (%)</td>
<td>1 (4)*</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Refractive error,</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in diopters, mean (range; SD)</td>
<td>-1.34 (-2 to 3.5; 0.10)</td>
<td>0.5 (-0.5 to 1.25; 0.07)*</td>
<td>-1.54 (-3 to 2.5; 0.16)</td>
</tr>
<tr>
<td><strong>At 1 month,</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>At 6 months,</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Visual acuity,</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in logMAR, mean</td>
<td>-0.57 (-1.5 to 1.75; 0.08)</td>
<td>0.5 (-1 to 1; 0.06)*</td>
<td>-0.84 (-1.75 to 2.5; 0.11)</td>
</tr>
<tr>
<td>(range; SD)</td>
<td>Scleral Fixated IOL (N=24)</td>
<td>Iris Claw IOL (N=26)</td>
<td>CM-T Flex IOL (N=23)</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------------------</td>
<td>-----------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td><strong>At 1 month</strong></td>
<td>0.49 (0 – 1.2; 0.15)</td>
<td>0.51 (0-1.2; 0.14)</td>
<td>0.47 (0-1.3; 0.13)</td>
</tr>
<tr>
<td><strong>At 6 months</strong></td>
<td>0.24 (0 – 1; 0.13)</td>
<td>0.29 (0-1.1; 0.16)</td>
<td>0.27 (0-0.77; 0.12)</td>
</tr>
</tbody>
</table>

Table 1. Complication profile encountered in the three groups

<table>
<thead>
<tr>
<th></th>
<th>Scleral Fixated IOL (N=24)</th>
<th>Iris Claw IOL (N=26)</th>
<th>CM-T Flex IOL (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corneal edema, N (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>At 1 month</strong></td>
<td>2 (8)</td>
<td>5 (21)</td>
<td>3 (13)</td>
</tr>
<tr>
<td><strong>At 6 months</strong></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>AC reaction, N (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>At 1 month</strong></td>
<td>4 (17)</td>
<td>6 (28)</td>
<td>6 (26)</td>
</tr>
<tr>
<td><strong>At 6 months</strong></td>
<td>1 (4)</td>
<td>4 (14)*</td>
<td>1 (6)</td>
</tr>
<tr>
<td><strong>Irregular pupil, N (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>At 1 month</td>
<td>At 6 months</td>
<td>Haptic exposure, N (%)</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>------------</td>
<td>-------------</td>
<td>------------------------</td>
</tr>
<tr>
<td></td>
<td>0 (0)</td>
<td>11 (42)**</td>
<td>0 (0)</td>
</tr>
<tr>
<td>At 6 months</td>
<td>0 (0)</td>
<td>11 (42)**</td>
<td>0 (0)</td>
</tr>
<tr>
<td>IOL dislocation, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 1 month</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>At 6 months</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>IOL tilt, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 1 month</td>
<td>0 (0)</td>
<td>2 (9)*</td>
<td>0 (0)</td>
</tr>
<tr>
<td>At 6 months</td>
<td>0 (0)</td>
<td>2 (9)*</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Vitreous haze, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 1 month</td>
<td>5 (21)</td>
<td>11 (43)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>At 6 months</td>
<td>1 (4)</td>
<td>4 (14)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Retinal breaks / detachment, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 1 month</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
Purpose: To compare ease of visualization and comfort of the surgeon during phacoemulsification surgery using NGENUITY® 3D (NG) visualization system and standard operating microscope (SOM).

Design:

A randomized, single-blind, prospective, single center study.
Introduction: Cataract is the leading cause of blindness accounting for 66.2% of blindness cases in India, as per the National Blindness and Visual Impairment Survey India 2015-2019.\(^1\) Phacoemulsification is one of the safest and preferred method of cataract surgery, performed since 1967.\(^2\) Optimal visualization of the anterior capsule, nucleus, cortex, and posterior capsule is one of the primary requirements of phacoemulsification.\(^3\) Surgical visualization using optical microscopy has been the standard for intraoperative surgical viewing since more than five decades. Although significant advances have been made in the optical quality, illumination and depth of field, several limitations still persist. These include dependence on oculars, low performance under high-magnification, use of dyes to highlight certain structures, ergonomics issues for surgeons, photo toxicity due to excessive light exposure, inability to display vitrectomy machine setting parameters through the oculars, and limited illumination of the visualization field in terms of brightness and contrast.\(^4,5\) Heads-up three-dimensional (3D) visualization systems enable surgeons to operate independent of the eyepieces of the standard operating microscope (SOM) replacing them with high-resolution visualization systems thereby improving the ergonomics. 3D high dynamic range technology and improved images under high-magnification allows lighting to be optimized across a wide range of brightness and darkness and permitting precision in the movement of instruments and manipulation of tissue within vitreous cavity. Additionally, digital video functionality has undergone rapid advancements in frame rate, pixel count and resolution, dynamic range, and latency over the past few years.\(^6\)
In NG, the captured images are processed using a 3D image processor and displayed on a 3D 4K OLED 55-inch display, which can then be viewed by the surgeon through a pair of passive, circular, polarized 3D glasses.\textsuperscript{5-8} Compared to SOM, NG platform results in up to 48% increased magnification, 5 times better depth of field, and up to 42% finer depth resolution (stereopsis) at the highest system magnification, 30% open aperture setting, and a viewing distance of 1.2 meters.\textsuperscript{7}

Till date, no study has focused on the benefits of a heads-up 3D system such as NG in terms of ease of visualization and comfort for the surgeon in the heads-up position. Thus, we conducted a prospective study to evaluate the above factors during phacoemulsification surgery using NG versus SOM (Zeiss OPMI Lumera I Operating microscope i060). A novel surgeon comfort score questionnaire designed in-house was completed by five senior cataract surgeons at the end of each surgical session to assess the ease of visualization and comfort enhancing the robustness of the data.

**Methods:**

Patients undergoing phacoemulsification surgeries were randomly assigned to two groups based on the visualization modality used: NG and SOM. A total of five surgeons operated on 224 patients having cataracts. Four surgeons operated on 17 patients each, with SIMC in the NG group and the SOM group; fifth surgeon performed 19 surgeries on SIMC patients in each of the NG and SOM groups. In total, 174 SIMC surgeries were performed for group NG and SOM, respectively, by the five surgeons. Additionally, each surgeon also operated on 10 patients having MC, 5 in NG group and 5 in the SOM group;
with the overall total of 224 patients.

Ease of visualization and comfort of the surgeon using different visualization systems was assessed using a 37-parameter surgeon comfort score questionnaire developed in-house.

**Statistical Analysis**

All randomized subjects were included in the effectiveness analyses. The statistical analysis was carried out using available data based on pooled data of all surgeons. Data was listed and descriptive analysis were provided by NG visualization system and SOM. Categorical data was summarized by means of absolute and relative frequencies (counts and percentage), quantitative data by means of the number of observations, mean, median, SD, and range (min, max). The 95% confidence interval was provided as appropriate. Effectiveness analyses included two-sided statistical testing for the primary endpoint (the ease of visualization of the surgeon while doing phacoemulsification procedure) using Kruskal Wallis test to compare two viewing modalities. Some of the parameters were analyzed using an independent t-test or Mann Whitney u test. Categorical variables between the two viewing modalities were compared using Chi-square ($\chi^2$)/Fisher's exact test of treatment group differences. Correlation coefficient was calculated using Spearman's rank correlation coefficient. Serious/adverse events were summarized.

**Results:**

A total of 224 phacoemulsification with intra ocular lens (IOL) implantation was performed in SIMC (n=174) and mature cataract patients (MC, n=50)
using NG and SOM as the visualization system. The intraoperative ease of visualization score of the surgeon while performing phacoemulsification was comparable between NG and SOM groups (4.92–5.00). The mean score for difficulty in using the 3D spectacles and fogging of the surgeon’s glass spectacles was in the range of 4.97–5.00 and 2.93–3.00, respectively. Hand eye coordination score was similar in the NG and SOM groups (4.97–5.00). Neck discomfort after the surgery was significantly high in all groups, with a comparatively lower discomfort in the NG group (score: 1.04 vs 1.56). The Spearman rank correlation coefficient (r) between illumination of the OT room and surgical field revealed a weak negative correlation for most of the patients in the NG group, and a positive correlation for patients in the SOM group. Surgeons needed lower illumination for surgery while working on NG compared to the SOM and surgeon comfort with the illumination was also higher with NG system. No correlation was obtained between brightness of the surgical field and comfort with the brightness of the surgical field.

Discussion:

This study was conducted to evaluate the ease of visualization of the surgeon using a 3D heads-up display system (Alcon Vision LLC, Fort Worth, TX, USA). In this study, we found the intraoperative ease of visualization of the surgeon to be similar using NG or SOM visualization system. However, the NG system required very low illumination of the surgical field as compared to SOM, thus reducing the risk of phototoxicity to the patients. Better ergonomics for the surgeon, superior visualization of the surgical field in low illumination, reduced phototoxicity for patients, good anatomic and visual outcomes, and
easy learning curve are some of the benefits of the 3D system. The earliest report on the use of a 3D visualization system in cataract surgery was in 2010 by Weinstock et al reporting excellent outcomes using both 3D system and conventional binocular microscope. The same group in 2019 reported comparable complication rate and surgical time between NG visualization system and SOM. The safety and usefulness of NG visualization system for cataract phacoemulsification and IOL implantation was reported recently. The 3D visualization system provides real-time intraoperative images of the surgical field with a short image latency. The latency documented for NGENUITY is in the range of 80 milliseconds between intraocular maneuvers and image displayed on screen compared to conventional microscope. Several studies have reported the latency to be insignificant for ophthalmic surgeries when compared with the conventional microscope. The almost similar ease of visualization score using the NG and SOM system was in corroboration with these study findings. High scoring of the difficulty in using the 3D spectacle revealed the relative ease the surgeons experienced while donning the 3D spectacle. Maintaining a clear operating field is one of the key elements while performing any surgical procedure and fogging of the surgeon’s glass spectacles can cause an obstacle in achieving this objective. Another significant advantage of the 3D visualization system is the decreased amount of light required to provide the enhanced visualization to the surgeon. Hamasaki et al. reported the successful use of NG system for strabismus surgery performed with only the room’s ambient light and without the microscope’s light source. Illumination reduction of the surgical field reduces the risk of renal photo toxicity for patients during the
surgery. A lower illumination was used for the NG system as compared to the SOM system enabling the surgery to be performed with a lower risk of phototoxicity in the former case. Likewise, the brightness of the surgical field was more for the SOM system than NG and surgeons reported more comfort using the NG system based on the comfort with brightness score. However, no correlation was obtained between brightness of the surgical field and comfort with the brightness of the surgical field. Most of the studies reported a comparable or lower rate of surgery duration using the NG system.

Conclusions:

Overall, ease of visualization of the surgeon using the NG system and SOM system were comparable. Most of the parameters were similar for the NG and SOM system; however, a relatively lower illumination of surgical field was required in case of the NG system. Innovations in the 3D visualization system, such as the NG system have automated cataract surgery, and may result in a transition from the SOM system to the heads-up display system in the future.

References


10. Weinstock RJ, Diakonis VF, Schwartz AJ, Weinstock AJ. Heads-up


ALL GUJARAT OPHTHALMOLOGICAL SOCIETY: QUARANTINE MYOPIC PROGRESSION IN SCHOOL CHILDREN AFTER COVID-19 HOME CONFINEMENT

Abstract

Outdoor activities are known to have protective effect on myopic progression. Due to the lockdown and home confinement after COVID-19 pandemic, the effect of this is unknown on myopic progression in children of school going age.

Materials and methods

All children between the age group of 6-12 years were included in the study. Cycloplegic refraction, axial length, corneal curvature and ocular parameters were measured and compared. These children were reviewed every 6
months and were not on any treatment for prevention of myopic progression.

Results

A total of 36 eyes of 36 children were included in the study. Twenty four were male and 12 were females. The mean age was 8.7 +/- 2.2 years. The median progression in myopia per year prior to lockdown (2019-20) was -0.75 D (interquartile range -0.5 D to -0.75D) and post lockdown (2020-21) was -1.25 D (interquartile range -1.0 D to -1.25 D).

The median progression in axial length per year prior to lockdown between 2019-2020 was 0.24 mm (interquartile range 0.15 mm to 0.37 mm) and post lockdown (2020-21) the median was 0.63 mm (interquartile range 0.54 mm to 0.78 mm).

Conclusion

The lockdown in COVID-19 pandemic has given a sharp rise in the myopic progression of children in one year.

Keywords

COVID-19 pandemic, quarantine, myopia, lockdown, myopic progression, school children Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was declared a pandemic by world health organization with more than 213 countries affected by it.[1] The lockdown in India was started on 25th March 2020 with a view to flatten the curve.[2] Myopia is associated with long hours of reading and screen time.[3-5] The lockdown and the imminent near work, along with increased digital screen time has raised a concern for
the myopia boom across the world. [6-8] Few studies have showed a substantial myopic shift in school going children after lockdown. [9,10] We present a review of children who were assessed before and after the home confinement during the lockdown and its effect on their myopic progression.

**Materials and Methods**

A total of 36 children between the age of 6-12 years were identified who were being followed up at Baroda Children Eyecare and Squint Clinic for last 2 years and were myopic children not on any kind of treatment for myopic progression. One eye was chosen using a random number table to avoid any bias. A retrospective review of records was done from October 2018 onwards. Children who were regularly followed at 6 months interval were included in the study. All the children were not on any intervention therapy for myopia.

The prelockdown (Mar 2019-Mar 2020) included children who had a one year followup and were using glasses regularly. The same set of patients were followed up during the lockdown period (Mar 2020- Mar 2021). The data was recorded and evaluated.

A detailed ophthalmic evaluation including visual acuity, cycloplegic refraction, keratometry, pupil size, axial length and orthoptic checkup was done which included cover test, near point of accommodation, fusional amplitudes and stereopsis assessment. All the examination details were recorded and analysed. Patients with contact lens, prior ocular surgeries were excluded from the study.

**Results**
The mean age of the 36 children was 8.7 +/- 2.2 years. Twenty four were male and 12 were females. The median progression in myopia per year prior to lockdown (2019-20) was -0.75 D (interquartile range -0.5 D to -0.75D) and post lockdown (2020-21) was -1.25 D (interquartile range -1.0 D to -1.25 D).

The median progression in axial length per year prior to lockdown between 2019-2020 was 0.24 mm (interquartile range 0.15 mm to 0.37 mm) and post lockdown (2020-21) the median was 0.63 mm (interquartile range 0.54 mm to 0.78 mm).

**Statistical Analysis**

Descriptive and inferential statistics were performed using STATA version 15 for Windows (StataCorp LP, College Station, Texas, USA). Shapiro Wilk test was used to check for normality of the variables. Data with nonnormal distribution were represented using median and the first and third quartiles (inter-quartile range). The Wilcoxon-Sign Rank test was used to compare the change in refractive error and axial length between the groups. A p value less than 0.05 was considered statistically significant.

**Discussion**

A direct correlation of near work, ocular strain, increase in indoor timing and increase in axial myopia has been described by various co-workers. [3-11] Sumitha et al. even predicted that a spurt of increase in myopia may be seen post lockdown. In their own out-patient department, they compared the visits of patients and concluded that there was a significant rise in refractive errors.[7] A similar increase was also noticed in the school screening
examinations for refractive errors.\textsuperscript{[9–10]} The limitation of their study was that it was unclear if the same set of children were reassessed, or it was a generalised study of the same age group of patients by Wang et al.\textsuperscript{[9]}

The description by Chang et al. has been more comprehensive wherein they divided their study into four rounds with three periods in between depending on the lockdown policies.\textsuperscript{[10]} The study had a large sample size but was more of a screening study conducted in schools. No cycloplegic refraction and biometry was performed in their study. It is important that biometry be made part of the myopia studies and management done in the clinic as suggested Hussaindeen et al.\textsuperscript{[11]}

The strength of our study is that it was done on a relatively large sample size and the same set of children were reassessed at multiple intervals without any loss to follow-up. Hence, we could show that the lockdown was one the important factor for the increase in the myopia and axial length. The reason for this increase in myopia could be implicated to increased indoor time along with increased screen time which is already a known risk factor for progression.\textsuperscript{[4, 11–13]} Outdoor time spent along with light exposure and dopamine levels have been discussed as the underlying mechanisms for myopic progression.\textsuperscript{[13–14]}

\textbf{Conclusion}

Our study shows that the myopic progression was significant during the quarantine period and therefore calls for strategies to prevent this. A program on the lines of National Myopia prevention program would help in creating awareness and detecting these children early to aid the prevention
of progression.

Limitation

Few limitations of our study are that it is retrospective in nature. A prospective study would be more desirable. Also an even larger sample size would be better. At this point since the lockdown was unpredictable and unplanned, we believe that these children can be followed up further and then reassessed again after few years to know the after effect of the same.

References


5. Huang HM, Chang DS, Wu PC. The association between near work


Table 1. Shows the progression over a period of 2 years in the diopteric power and axial length

<table>
<thead>
<tr>
<th></th>
<th>Pre lockdown (March 2019-March 2020)</th>
<th>Post lockdown (March 2020-March 2021)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myopic progression (in D)</td>
<td>-0.75 D</td>
<td>-0.5 D to -0.75 D</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>-1.25 D</td>
<td>-1.0 D to -1.25 D</td>
</tr>
<tr>
<td>Axial length progression (in mm)</td>
<td>0.24 mm</td>
<td>0.15 mm to 0.37 mm</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>0.63 mm</td>
<td>.54 mm to 0.78 mm</td>
</tr>
</tbody>
</table>
This paper was judged as the BEST PAPER of
Community / Social Ophthalmology – II

Dr. MAHESHWARI S

TRASH TO TREASURE RETCAM- TREASURE TO SAVE SIGHT AMIDST PANDEMIC

Abstract:

To evaluate diabetic retinopathy (DR) screening at vision centres in rural and underserved areas in Tamil Nadu. Teleophthalmology screening and referral for patients with Diabetic retinopathy from 11 vision centres within a time span of 6 months. Known and newly diagnosed diabetic patients presenting with history of reduced vision were subjected to dilated fundus evaluation with trash to treasure RETCAM by trained optometrists. Patients were diagnosed and graded DR by a remote expert. Of the 1904 patients presenting to vision centres, 851 (45%) patients were diabetics. 72(8%) patients were diagnosed with DR changes of which 49 (69%) patients were immediately referred to higher centre for further management. Trash to treasure RETCAM is a simple DIY smart phone based fundus imaging tool which can help in remote diagnosis of fundus pathology in an efficient way during this pandemic times eliminating unnecessary referrals.

Introduction:

Diabetes mellitus (DM) is a global epidemic. Its prevalence in India has increased from 61.3 million in 2011 to 77 million in 2019; a further 77 million are considered to be prediabetic and is projected to grow to a 101
million by 2030 and 134.2 million by 2045\textsuperscript{1,2}. With over 77 of the 463 million people suffering from diabetes mellitus (DM) globally residing in India, it is said to be the diabetic capital of the world\textsuperscript{3}.

Diabetic retinopathy is the most common ocular microvascular complication\textsuperscript{4}. The National Survey 2015–2019 reported that 16.9\% of those with DM had diabetic retinopathy (DR) in India, and 3.6\% had Sight-threatening DR (STDR)\textsuperscript{5}. The progression of the disease is diagnosed through different stages ranging from Very Mild Non-Proliferative diabetic retinopathy (VMNPDR) to Moderate Non-Proliferative diabetic retinopathy (MODNPDR) stages, which are largely asymptomatic, to severe NPDR and proliferative diabetic retinopathy stages, which are potentially blinding if left untreated\textsuperscript{6}. Proliferative DR and diabetic macular oedema are two main sight-threatening components of DR (STDR)\textsuperscript{7}.

According to the WHO, screening should be done for diseases that are an important health problem, have effective treatment which is possible to be delivered early, before the appearance of symptoms, technology for diagnosis is available, screening is feasible and cost effective, and subjects can be followed longitudinally. Diabetic retinopathy screening meets the World Health Organization (WHO) criteria for screening programs\textsuperscript{8}.

Screening for DR is essential as individuals with DR are often asymptomatic during the earlier stages\textsuperscript{7}. It is recommended that DR screening be done for all people with known diabetes on treatment, a single record of random blood sugar (RBS) of ≥ 200 mg/dl (≥11.1 mmol/l), glycated haemoglobin (HbA1C) > 6.5\% (48 mmmol/l) or higher or gestational diabetes when first
notified to a medical personnel\textsuperscript{9}. Early detection of DR by regular screening can help in slowing the progression of any DR to STDR with good control of modifiable risk factors like hyperglycaemia, hypertension, and treatment of dyslipidaemia\textsuperscript{10}.

Various models of DR screening applied in India are: 1) Hospital based screening model, 2) community-based screening model, 3) Teleophthalmology Screening model\textsuperscript{10}.

At present situation of pandemic, Teleophthalmology plays a very important role in screening of DR patients by bridging the gap of distance, time and burden on manpower.

The available devices for screening of DR can be divided into table-top and smartphone-based devices\textsuperscript{11}.

The gold standard for grading the severity of DR is stereoscopic fundus photography through dilated pupils, using seven standard fields, and grading guidelines for these photographs established by the Early Treatment Diabetic Retinopathy Study (ETDRS) group\textsuperscript{12}. Smartphone based retinal imaging system, is reasonably sensitive and specific in detecting diabetic retinopathy of varying severity and can be tried as an effective screening tool for diabetic retinopathy.\textsuperscript{10}

T3 Retcam is one such Do It Yourself smartphone based imaging modality used for screening various retinal pathologies. This device was supplied to these centres which could not afford higher fundus imaging devices. Trash To Treasure Retcam remained the only option for screening.
To evaluate diabetic retinopathy (DR) screening using T3Retcam at vision centres in rural and underserved areas in Tamil Nadu for tele ophthalmology during the pandemic.

**Materials and methods:**

It is a prospective hospital-based study conducted at 11 vision centres over the time span of 6 months (January 2021 – June 2021)

Study participants were known and newly diagnosed diabetic patients presenting to vision centre. Informed and written consent were obtained.

Detailed history of patients regarding name, age, sex, occupation, and address; drug history; any history of trauma or inflammation, presenting symptom, duration, and associated conditions; and medical history were recorded.

Visual acuity and refraction were assessed using an illuminated Snellen’s chart, and the ETDRS classification system was used to classify the best-corrected visual acuity.

Ocular examination was done to rule out any abnormality in the lids, conjunctiva, cornea, anterior chamber depth, iris, pupil, and lens with a torchlight.

The patients were then taken up for fundus photography by T3 Retcam which were operated by trained technicians. (Picture 1)

The images were then analysed remotely by Retinal surgeon and grading was done with Early Treatment Diabetic Retinopathy Study (ETDRS) grading system.
Patients requiring intervention were then referred to tertiary hospital.

Results:

Over a period of 6 months, 1904 patients visited 11 vision centres. Out of which 851 diabetics (44.69 %) were screened for Diabetic retinopathy changes. 11 patients were known diabetic retinopathy and 61 patients were newly diagnosed with diabetic retinopathy. Of the 72 patients with diabetic retinopathy, 49 patients were referred to tertiary eye hospital for further examination and management. The mean age of patients in the study group was 54.4+/-8.2 years.

Out of 49 referred patients 35 patients visited retina clinic and rest were lost to follow up. 56 eyes of 35 patients were diagnosed to have vision threatening diabetic retinopathy and was referred in need of treatment to tertiary hospital. After clinical examination and multimodal imaging at retina clinic in tertiary hospital 45 eyes i.e., 80.35% were advised treatment.

Out of 45 eyes, 11 eyes required Panretinal photocoagulation (PRP), 19 eyes required intravitreal Anti-VEGF and steroid injections, 6 eyes required intravitreal injections and PRP, 9 eyes needed surgery. (Graph 1)
Discussion:

Teleophthalmology plays an important role in screening of many diseases, DR being one of the most important ocular disease among them. Preventive care of DR focuses on screening of retinal images to evaluate the presence or absence of DR or sight-threatening DR. It is part of routine annual diabetes preventive care. Diagnostic care involves treating or investigating sight-threatening DR. It may include treatment for diabetic macular oedema or proliferative diabetic retinopathy (PDR), ongoing care of patients with DR, and multimodal imaging tests needed to manage or treat DR. Smartphone based devices play important role in preventive care of DR.

T3Retcam is one of such smart phone based device. Taking into consideration of the simplicity, stability, and affordability of the device; nevertheless, the portability, data storage capacity, and wireless connectivity of the smartphone make the T3 Retcam an important tool for screening of retinal disease. The T3R is shown to have a sensitivity of
88.4% and a specificity of 100% when compared with direct ophthalmoscope. The Trash To Treasure Retcam has been able to pick up larger findings/signs (Dot and Blot haemorrhage, hard exudate, soft exudate, superficial haemorrhage, IRMA, NVE, NVD, Tractional bands, Laser marks, CSME) which pose a threat to the vision. Although it is known to misdiagnose cases of VMNPDR group due to chances of missing microaneurysms 15.

Due to COVID-19 pandemic, there has been compromise in medical care, including screening programmes.16 Patient coming for routine DR check-up and screening to retina specialists has been affected in view of travel restrictions and escalating infections. In areas with effective infection control and low community transmission it is believed that DR screening can be continued safely, especially when incorporating advances in telemedicine.17

Pre-specialist diagnostics will identify healthy eyes, make a diagnosis and recommend a referral only if intervention is required. This will make the system less dependent on expensive human resources and will lead to optimal use of current resources which is of utmost importance during the pandemic.

Screening Diabetic patients at vision centres using T3Retcam associated with multi-speciality eye hospital is a very good alternative during COVID 19 outbreak.

Conclusion:

T3 Retcam is an inexpensive, quick, convenient, and portable device, with high sensitivity, specificity, and diagnostic accuracy for diabetic screening. It
helps reduce morbidity of patients who are at a high risk of vision loss during pandemic situation.

REFERENCES


9. Raman, Rajiv; Ramasamy, Kim1; Rajalakshmi, Ramachandran2; Sivaprasad, Sobha3; Natarajan, S4 Diabetic retinopathy screening guidelines in India, Indian Journal of Ophthalmology: March 2021 - Volume 69 - Issue 3 - p 678-688 doi: 10.4103/ijo.IJO_667_20


PICTURE 1: A: Hard exudates at macula suggestive of Clinically significant macular oedema, B and C: Fibrous proliferation with Neovascularisation at arcades suggestive of Proliferative Diabetic Retinopathy, D: Early fibrous proliferation at disc suggestive of Proliferative diabetic retinopathy.
4 YEAR LONGITUDINAL STUDY OF 44535 INDIVIDUALS TO SEE REDUCTION IN BLINDNESS & VISION IMPAIRMENT.

Abstract

Aim:

To estimate the prevalence of blindness and severe visual impairment (SVI) using a door-to-door screening and vision centre (VC) examination strategy in an urban area in western Maharashtra (Pune), India and to repeat the exercise after 4 years to study its impact.

Methods:

Four trained community health workers measured visual acuity and performed an external ocular examination in patients’ homes. People with vision <6/18 were requested to visit the VC for a comprehensive eye examination by an optometrist. An ophthalmologist examined people who did not improve to 6/12. A home examination was done for people who did
not visit the VC despite two requests. The same population was examined twice in an interval of four years.

Results:

In the study 44,535 people in 2015-16 and 98.14% (n= 43,708) of them in 2018-19 were examined. Blindness (vision < 3/60 in better eye), and moderate-to-severe visual impairment (MSVI, vision 6/18- 6/60 in better eye) were 0.26% and 1.3% respectively in first cohort; and 0.16% and 1.1% respectively in second cohort (P<0.001). When the worse eye was considered, the prevalence of blindness reduced from 0.72 to 0.44%, SVI reduced from 0.1% to 0.07%, and MVI decreased from 1.7% to 1.49% between 2015 and 2019 (P<0.001). Females (P<0.001) and older individuals (P<0.001) were more likely to have blindness or SVI. In the VC, 8211 people were examined in four years.

Conclusion:

The reduction of blindness and MSVI in the urban area of Pune could be partly ascribed to the presence of a vision centre and attendant screening in this locality.

Introduction

Over five decades, India has conducted several surveys to measure the magnitude of blindness and visual impairment (VI). Considering all age groups, the prevalence of blindness was 1.39% (with <6/60 as blind) in the 1971 ICMR (Indian Council of Medical Research) survey and 0.36% (with <6/60 as blind) in the 2019 NPCB VI (National Program for Control of
Blindness and Visual Impairment) survey. With the <6/60 criteria, the figure was 0.71%. In people over 50 years, the prevalence of blindness (presenting vision <6/60 in better eye) was 8.5% (95% CI: 8.1 to 8.9) as per the nationwide survey in 2009. The World Health Organization (WHO) uses presenting vision <3/60 in the better eye for international comparisons. Using this cut off, the prevalence was 5.34% (95% CI: 5.06 to 5.62) [1-4]. This downward trend in blindness and VI in India has been possible due to the combined efforts of the government, non-governmental organisations and numerous private practitioners. [5]

We collected eye health data from people living in an urban slum/low-income area in Pune city (Maharashtra, India) through two-time points – 2015-16 and 2018-19. We conducted a door-to-door screening of the entire population/community and complemented it with further diagnosis and treatment in a vision centre established in the locality. This communication is a report of the population-based eye care modelled/delivered through the vision center.

Methods

The protocol was reviewed and approved by the institutional ethics sub-committee of Dr. D.Y.Patil Medical College (IESC/FP/2019/05). The study adhered to the tenets of the declaration of Helsinki for the study of human subjects.

This study had two-time points, 2015-16 and 2018-19, from the project implemented on Operation Eyesight’s flagship Hospital-Based Community Eye Health model. At the first time point, eye screening of the designated
slum/low-income population of Pune city was conducted by a door-to-door survey. Before the study, community health workers (CHWs) recruited from the same community were trained on communication skills and eye examination techniques. Trained CHWs compiled the demographic data and measured the visual acuity of individuals in their homes using Snellen's charts/Landolt C charts and referred individuals with less than 6/18 in any eye to the VC, located within 2 km from their residence. At the VC, an optometrist performed a comprehensive eye examination of both eyes for these people.[6] An ophthalmologist further examined those whose vision did not improve beyond 6/12. The ophthalmologist assigned a cause of the vision impairment and/or blindness to those whose vision did not improve beyond 6/60. The ophthalmologist categorized the causes of visual impairment/blindness into an avoidable (preventable or treatable) or a non-avoidable cause. The avoidable one was considered as the cause of blindness when both the causes were present. Untreatable blind patients were assisted in obtaining disability (seeing-blindness) certificates from government authorities.

The optometrist visited the homes of people with vision impairment if they did not visit the VC. These people were again requested to visit the VC for a consultation with the ophthalmologist. The ophthalmologist made a home visit to people who still did not visit within a week of the optometrist's examination. The optometrists, equipped with hand-held devices such as an auto-refractometer (Plus Optix), handheld slit lamp (Kanghua), and rebound tonometer (I-care), made home visits; the ophthalmologist, when visited, also carried all these equipment, and additionally, an
ophthalmoscope (Heine, Germany) and prism bar, to confirm the diagnosis. The initial assessment was done from January 2015 to July 2016. The ophthalmologist, optometrist for the first two years, the social worker cum co-ordinator, and the four CHWs were all females.

A repeat examination of the same population was performed from May 2018 to March 2019. The survey processes were essentially similar to the first component of the study. The CHWs collected demographic details of each family member (age, gender, occupation, and place of work, history of systemic illness, known disability, pregnancy, and lactation). They also documented migration, further disability, and death. The comprehensive eye examination by the optometrist and ophthalmologist in 2019 was similar to the one done in 2015-16.

**Results**

Four trained CHWs recorded vision and collected other data from the population block in the Yerawada-Vishrantwadi ward of Pune Municipal Corporation in 2015. At the first time point, 44,535 individuals of 9,213 households were examined, and at the second time point, 43,708 (98.1% of the first cohort) individuals of 9039 (98.1% of the first cohort) households were examined. In either cohort, there were 49.8% males.

In the 2015-16 survey, 1.7% (n= 740 of 44535) people had visual impairment (visual acuity < 6/18), and 118 people (0.26%) were blind in the better eye. (Table 1) In the 2019 survey, 1.3% (n= 556 of 44708) people had visual impairment or other symptoms in the home screening; 95 of them (0.21% of the sample) had blindness and SVI, and 72 (0.16%) people were
blind in the better eye. In the first (2015-16) cohort prevalence of blindness (<3/60), SVI (3/60-<6/60), and visual impairment (6/60-6/24) in the better eye for the 51-70-year-olds was 0.8%, 0.6%, 6.9%, respectively; and for 70+ year olds was 5%, 0.9%, 10.5% respectively. Additionally, 71 children had failed the test by the CHWs; the optometrist examined them, and 21 required examinations by the ophthalmologist.

On re-survey and examination in 2019, a total of 827 people were not examined for the following reasons: 222 had died, 396 had moved to another locality, 28 refused repeat examination and 181 were lost to follow-up. In this cohort, 72/43708 (0.16%) had vision <3/60 in the better eye, and 23 (0.05%) had vision between 3/60 to 5/60. 94.2% had vision ≥6/12 in the better eye in 2019.

Between the two-time points, the prevalence of blindness reduced from 0.26% to 0.16, SVI halved (0.1% to 0.05%), and MVI decreased from 1.3% to 1.1% in the better eye. (Table 1)

Table 2 shows the number and spectrum of people with blindness in the 2015-2016 and 2018-19 periods. The principal cause of blindness was cataract, with a proportion of 44.9% and 41.6% in the first and second surveys, respectively.

**Discussion**

Population-based studies are required to assess the magnitude of eye problems and the allocation of available resources. Because as most of the blindness and visual impairment occurs in older adults, rapid methods recruit people at least 40 years of age and older. [7]
Our longitudinal eye health study of the urban low-income population in Pune (India) city showed that the prevalence of blindness and VI reduced over four years, blindness from 0.26% to 0.1% and VI from 0.16% to 0.05%. Women continued to have a higher prevalence of blindness at both time points. The gender gap was narrowed after four years, but the difference persisted. Also the average age of the population had increased by four years, but the prevalence had still reduced. We also observed that more women visited the VC. We attribute both phenomena – a greater number of people available for a repeat eye examination after four years and more females seeking eye care – to the nudging of people through the door-to-door survey and the existence of VC (served by predominantly female staff) in the vicinity that provided eye care throughout the year.

A rapid assessment of avoidable blindness had been done in urban Pune in 2016. This study examined 3,221 individuals aged >50 years, with 80% in the lower-income group. The age- and sex-standardized prevalence of blindness was 1.3% (95% CI 0.9 -1.8). Cataract was the most common cause of blindness (45.7%), followed by overall posterior segment disorders (39.1%).[8] The findings of the current study were similar.

Limitations of this study: We did not measure inter-observer agreement in vision recording. The illumination may have varied in the homes, verandas, and streets, even if the distance was ensured with a string or tape. We did not measure the quantum of illumination.

Our model of combining screening and care with eye disease survey and longitudinal surveillance add an additional advantage to IPEC. The proximity
of the vision centre provides incentives for people to return for examination and removes the gender and age barriers for accessing eye care. We anticipate that future epidemiological studies might use this model for service delivery and eye disease prevalence studies.

References:

1. Indian Council of Medical Research. The prevalence and causes of blindness in India. 1971


Table 1: Visual acuity of examined individuals in 2015-16 and 2018-19 (better eye).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>&lt;3/60</th>
<th>3/60-6/60</th>
<th>6/60-6/24</th>
<th>≥ 6/18</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>118 (0.26%)</td>
<td>43 (0.1%)</td>
<td>579 (1.3%)</td>
<td>43795 (98.3%)</td>
<td>44535</td>
</tr>
<tr>
<td>2019</td>
<td>72 (0.16%)</td>
<td>23 (0.05%)</td>
<td>460 (1.1%)</td>
<td>43153 (98.7%)</td>
<td>43708</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>51 (0.2%)</td>
<td>20 (0.1%)</td>
<td>237 (1.1%)</td>
<td>21880 (98.6%)</td>
<td>22188</td>
</tr>
<tr>
<td>2019</td>
<td>32 (0.1%)</td>
<td>8 (0.0%)</td>
<td>176 (0.9%)</td>
<td>21559 (99.0%)</td>
<td>21775</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>67 (0.3%)</td>
<td>23 (0.1%)</td>
<td>342 (1.5%)</td>
<td>21915 (98.1%)</td>
<td>22347</td>
</tr>
<tr>
<td>2019</td>
<td>40 (0.2%)</td>
<td>15 (0.0%)</td>
<td>281 (0.9%)</td>
<td>21597 (98.5%)</td>
<td>21933</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>2015</td>
<td>2019</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>-----------------</td>
<td>-----------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3825 (100.0%)</td>
<td>3825</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-18</td>
<td>1 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10480 (99.9%)</td>
<td>10487</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19-30</td>
<td>7 (0.1%)</td>
<td>1 (0.0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11879 (99.8%)</td>
<td>11904</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31-50</td>
<td>13 (0.1%)</td>
<td>4 (0.0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12415 (98.9%)</td>
<td>12552</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>51-70</td>
<td>38 (0.8%)</td>
<td>27 (0.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4186 (91.7%)</td>
<td>4564</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;70</td>
<td>59 (5.0%)</td>
<td>11 (0.9%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>979 (83.5%)</td>
<td>1172</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age missing</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>31 (100%)</td>
<td>31</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head of Family</td>
<td>51 (1.3%)</td>
<td>12 (0.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3796 (94.7%)</td>
<td>4010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3643 (95.7%)</td>
<td>3807</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Members</td>
<td>67 (0.2%)</td>
<td>31 (0.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>39999 (98.7%)</td>
<td>40525</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>39513 (99.0%)</td>
<td>39901</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The visual disability grades were significantly different in the cohort of 2015.
compared to 2019, Chi-square = 26.6 degree of freedom = 3, p <0.001.

The visual disability grades were significantly different among males (Chi square = 14.7 degree of freedom = 3, p = 0.0001) and females (Chi square = 13.3 degree of freedom = 3, p = 0.0003) when compared to 2015 to 2019.

This variation of visual disability grade in two screening years was more among females compared to males.

Table 2. Causes of blindness (VA < 3/60) in two-time point cohorts

<table>
<thead>
<tr>
<th>Causes</th>
<th>2015-16 n=118</th>
<th>2018-19 n=72</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phthisical Eye</td>
<td>6(5%)</td>
<td>5(6.9%)</td>
<td>0.594</td>
</tr>
<tr>
<td>Anophthalmos</td>
<td>2(2.5%)</td>
<td>2(2.8%)</td>
<td>0.614</td>
</tr>
<tr>
<td>Optic Atrophy</td>
<td>3(1.6%)</td>
<td>2(2.8%)</td>
<td>0.922</td>
</tr>
<tr>
<td>Cataract</td>
<td>53(44.9%)</td>
<td>30 (41.6%)</td>
<td>0.661</td>
</tr>
<tr>
<td>Pseudophakia Refraction</td>
<td>8(6.8%)</td>
<td>8(11.11%)</td>
<td>0.297</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>11(9.3%)</td>
<td>8(11.11%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Diabetic Retinopathy</td>
<td>2(2.5%)</td>
<td>2(2.8%)</td>
<td>0.614</td>
</tr>
<tr>
<td>Refraction</td>
<td>8(6.8%)</td>
<td>4(5.6%)</td>
<td>0.736</td>
</tr>
<tr>
<td>Unknown</td>
<td>13(11%)</td>
<td>4(5.6%)</td>
<td>0.201</td>
</tr>
<tr>
<td>Corneal Causes</td>
<td>9(7.6%)</td>
<td>7(9.7%)</td>
<td>0.614</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>3(1.6%)</td>
<td></td>
<td>0.173</td>
</tr>
<tr>
<td>Total</td>
<td>118 (100%)</td>
<td>72 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

P-value > 0.05 (Not Significant) Chi-square test used
NOVEL ARTIFICIAL INTELLIGENCE (AI) DERIVED DRY EYE ANALYZER – IS IT HERE TO STAY?

ABSTRACT

Purpose:

To evaluate the role of novel AI derived dry eye analyzer in evaluation of patients with ocular surface disorder (OSD).

Method:

Prospective study to evaluate consecutive patients with OSD. They were subjected to Dry Eye work up by Dry Eye Analyzer including Non-invasive breakup time (NIBUT), Non-invasive Tear meniscus height, evaluation of meibomian gland function by built in infrared lighting & lipid layer thickness. Schirmer Test & ocular surface staining were also done for correlation.

Results:

250 patients with mean age 36.4±12.3 years were examined. According to
the Schirmer test severe dry eye was found in 11.6%. NIBUT revealed dry eye in 18.8%. Meibomian gland disorder was found in 56%. Abnormal lipid layer thickness was found in 51.6%. Abnormal tear meniscus height was found in 9.4%. Correlation coefficient between Schirmer & NIBUT was 0.7.

Conclusion: Dry Eye Analyzer can diagnose cases hithero missed by conventional tests & has the advantage of being non invasive.

INTRODUCTION

Dry eye disease (DED) is a frequent cause of ocular irritation for which patients seek ophthalmic care. Due to wide variety of presenting symptoms, it is often unrecognised. We come across many patients with ocular surface discomfort for whom empirical dry eye therapy is administrated most of the time without confirming whether the symptoms are attributable to a true dry eye condition.

The ocular surface consists of conjunctival mucosa that lines the bulbar and palpebral surfaces, the corneal scleral limbus, the corneal epithelium and tearfilm. These components work physiologically along with eyelids and lacrimal functional unit (LFU) to maintain a healthy ocular surface and form an "ocular surface system" Dry eye is a common disorder of the preocular tear film that results in damage to the ocular surface and is associated with symptoms of ocular discomfort. It is defined as a multifactorial disease of tears and ocular surface results in symptoms of discomfort, visual disturbance and tear film instability with potential damage of the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.\(^1\)
Though the definition of the disease is seemingly clear, the diagnosis presents multiple challenges to the clinician. First of all, no gold standard tests for diagnosis exists and no single test is sufficient for diagnosis due to poor reliability, multiple causes of the disease and lack of well-defined cut-off values to distinguish disease from normal. Secondly, the signs and symptoms do not always correlate and both can vary based on influences, such as diurnal or seasonal fluctuations. In addition, many of the tests are invasive in nature and this may influence the outcome. Lastly, other conditions can mimic dry eye such as ocular allergy. Due to these challenges, alternatives to traditional dry eye testing have emerged.

Many tests used in the diagnosis of DED rely on an experienced observer for image interpretation, which may be considered subjective and can result in diagnostic dilemma. Since artificial intelligence (AI) systems are capable of advanced problem solving, use of such techniques could lead to more objective diagnosis. Recent success in application of AI to medicine is mainly due to advancements in the sub-field of machine learning, which has enabled to automatically classify images and predict medical outcomes. Powerful machine learning techniques have been utilized to understand nuances in patient data and medical images, aiming for consistent diagnosis and stratification of disease severity. The purpose of this study is to evaluate the role of novel AI derived dry eye analyzer in evaluation of patients with ocular surface disorder (OSD).

**Methods**

A prospective study was conducted to evaluate consecutive patients with...
OSD. The study was approved by the Ethics Committee of our hospital and was performed in accordance with the guidelines of the Declaration of Helsinki. Informed consent was obtained from the study subjects at the time of enrolment. A total of 250 consecutive patients attending ophthalmology OPD with ocular surface symptoms were included. Exclusion criteria – Post operative patients

Patients suffering from acute ocular infections, extensive corneal or conjunctival pathology.

**Chronic dacryocystitis**

Patients who were on topical lubricants for the last six months.

Before tests some questions were asked to the patients regarding various symptoms they were suffering. A detailed history taking was done followed by slit-lamp biomicroscopic examination. They were subjected to Dry Eye work up by Dry Eye Analyzer including Non-invasive breakup time (NIBUT), Non-invasive Tear meniscus height, evaluation of meibomian gland function by built in infrared lighting & lipid layer thickness. Schirmer Test & ocular surface staining were also done for correlation.

**Non invasive break up time**

We used the novel AI derived dry eye analyzer (Dry eye diagnostic system, Mediworks) to assess the NIBUT. It uses Placido ring projection system with visible light to do NIBUT examination. The examination scope is up to 8mm corneal diameter which brings much more comprehensive diagnostic outcome. It notes image distortion and time from opening the eyes to the first sign of image distortion. After taking one video, it automatically
acquires the first break up time, average break up time, break up distribution, break up area, percentage curve and time distribution.

Grade 0 Normal, First Rupture Time: 10 s Average Rupture Time: 14 s
Grade 1 Warning, First Rupture Time: 6-9 s Average Rupture Time: 7-13 s
Grade 2 Dry eye, First Rupture Time: 5 s Average Rupture Time: 7 s

The normal time for TBUT is 15-20 seconds and TBUT with values less than 10 seconds suggest an abnormal tear film, with values 5-10 seconds considered marginal and less than 5 seconds indicative of dry eye.

Non-invasive Tear meniscus height

A video is taken and AI identification system depicts Tear Meniscus area and measures the tear height automatically with a built in ruler. It is measured in line with the pupil centre. It evaluates tear secretion amount and continuity objectively. Normal tear meniscus height is ≥0.2mm.
Meibomian gland function

Meibomian gland disease is a major, and perhaps the most common, etiologic factor in the pathogenesis of many subtypes of DED. Clinical diagnosis is often limited to examination of the lid margin by slit lamp to assess the degree of inspissation and telangiectasias, as well as subjective assessment of meibomian gland openings and meibum quality. Recently, infrared based non-contact imaging modalities of meibomian gland have offered detailed imaging to guide the diagnosis and treatment of MGD-related DED. Unique Built-in infrared lighting system provides a larger scope of capturing Meibomian gland image of both upper and lower lids.

Meibomian gland dropout as assessed by this method correlates well with signs and symptoms of dry eye disease. These imaging modalities can provide valuable objective information about the integrity of the glands. Adjustable depth of field makes the glands more prominent and distinguishable against the background.

Grade 0: No Meibomian Glands Loss
Grade 1: Meibomian Glands Loss < 1/3

Grade 2: Meibomian Glands Loss 1/3-2/3

Grade 3: Meibomian Glands Loss >2/3

Fig 5: No Meibomian gland loss

Fig 6: Grade 2 Meibomian gland loss
Lipid layer thickness

The principle of white light interferometry is used to get a quantitative value of lipid layer thickness. The patient is instructed to blink while a recording is taken. Thicker lipid layers are indicated by the bronze reflections with lot of colourful fringes. White colourless reflections are observed in patients with thin lipid layer.

Grade 1: <30
Grade 2: 30-60
Grade 3: 60-80
Grade 4: >80

(Unit: nm)

Schirmer test

It is the most commonly used test for the assessment of tear secretion. It
measures total tear secretions. It is performed with help of a 5x35 mm strip of Whatman-41 filter paper which is folded 5 mm from one end and kept in the lower fornix at the junction of lateral one-third and medial two-thirds. The patient should close his/her eyes up to 5 minutes. After 5 minutes wetting of the filter paper strip from the bent end is measured. Normal values of Schirmer-1 (without anaesthetic) test are more than 15 mm. Values of 5-10 mm are suggestive of moderate to mild dry eye and less than 5 mm of severe dry eye.

**Ocular surface dye staining**

Use of dyes can help assess the superficial ocular surface to detect damage that is often present in DED. We used fluorescein and lissamine green. Fluorescein dye is taken up by corneal and conjunctival tissue where there is disruption in the intercellular junctions. The staining of the cornea is seen with use of the cobalt blue filter on the slit lamp whereas the conjunctival staining is seen with a yellow (blue-free) filter. The classical staining of the cornea in dry eye includes superficial punctate keratitis concentrated in the intrapalpebral or inferior area initially. Lissamine green evaluates the conjunctival surface by staining areas not properly covered by mucin. The Oxford grading scale was used.\(^7\)

**Results**

250 patients with symptoms of OSD were examined. Mean age was 36.4±12.3 years. There were 167 females (66.8%) and 83 males (33.2%). According to the Schirmer test, severe dry eye was found in 11.6% patients and mild to moderate dry eye was found in 39.2%. NIBUT revealed dry eye
in 18.8% patients. Meibomian gland disorder was found in 56%. Abnormal lipid layer thickness was found in 51.6%. Abnormal tear meniscus height (TMH) was found in 9.4%. Ocular surface staining was found positive in 12.8% patients. Correlation coefficient between Schirmer & NIBUT was 0.7. 23.2% patients who had complaints of OSD showed negative results in all parameters of testing. 76.8% were diagnosed to have dry eye in one or more of the parameters. Only 9.2% patients tested positive in all the parameters. 14.4% patients who had normal values in Schirmer test and showed normal staining were diagnosed to have some form of tear film deficiency when tested by the AI derived Dry eye analyzer.

![Fig 8: Percentage of patients having dry eye Vs no dry eye](image1)

![Fig 9: Percentage of patients with various tear component deficiency](image2)
DISCUSSION

AI application in conjunctiva and tear film mainly focus on the diagnosis of dry eye. The diagnosis of dry eye is complicated and there is not a single perfect reference standard of it. Instead, a variety of examinations can provide supportive information. DED is one of the most common eye diseases worldwide, with a prevalence of between 5 and 50%, depending on the diagnostic criteria used and study population.

DED is divided into two subtypes defined by the underlying mechanism of the disease: (i) aqueous deficient DED, where tear production from the lacrimal gland is insufficient and (ii) evaporative DED (the most common form), which is typically caused by dysfunctional meibomian glands in the eyelids.

Artificial intelligence (AI) was defined in 1955 as “the science and engineering of making intelligent machines”, where intelligence is the “ability to achieve goals in a wide range of environments” McCarthy2006 AI proposal.

In our study, 23.2% patients who had complaints of OSD showed negative results in all parameters of testing and DED was ruled out in them. 9.2% patients were considered to be having severe DED when all the diagnostic tests such as NIBUT, Non-invasive Tear meniscus height, evaluation of meibomian gland function, lipid layer thickness, Schirmer Test & ocular surface staining showed positive results. Our study reported high positivity of Meibomian gland disorder (56%) and Abnormal lipid layer thickness (51.6%) which is otherwise missed by conventional testing methods.
CONCLUSION

Novel artificial intelligence derived Dry Eye Analyzer can diagnose cases hitherto missed by conventional tests & has the advantage of being non invasive. It has the potential of replacing the conventional invasive dry eye tests in the present times when both patients and clinicians want to maintain safe distance and prioritize on sanitization methods.

REFERENCES


10. ARVO Annual Meeting Abstract | July 2018

Diagnosis of dry eye subtype by artificial intelligence software based on the interferometric fringe pattern of the tear film obtained with the Kowa DR-1α instrument Reiko Arita; Katsumi Yabusaki; Takanori Yamauchi; Tadashi Ichihashi; Naoyuki Morishige Investigative Ophthalmology & Visual Science July 2018, Vol.59, 1965. doi:
BIHAR OPHTHALMOLOGICAL SOCIETY: MILTEFOSINE RELATED KERATITIS: CLINICAL CHARACTERISTICS AND MANAGEMENT

Introduction:

Leishmaniasis is a group of diseases caused by parasitic protozoa of the genus Leishmania, which is transmitted by phlebotomine sandflies. Three forms of leishmaniasis are recognized - cutaneous leishmaniasis, mucocutaneous leishmaniasis, and visceral leishmaniasis (VL). The VL is also known as kala-azar or black fever. In 10-20% cases, VL results in dermal complication called Post kala-azar dermal leishmaniasis (PKDL) characterized by a macular, maculopapular, and nodular rashes in skin which tends to appear 2–3 years post-treatment due to persistence of parasites in the skin after inadequate treatment.1-3 In Indian subcontinent, untreated cases of VL and PKDL are considered to be the sole reservoir of infection. PKDL is endemic in the states of Bihar, Jharkhand, West Bengal, Uttar Pradesh, with estimated PKDL prevalence ranging from 4.4 to 7.8 per 10 000 in Bihar.4-5
Currently, miltefosine, Sodium stibogluconate, and liposomal amphotericin B are recommended by the World Health Organization (WHO) as treatment options for PKDL, however, miltefosine remains as the only oral drug highly effective against PKDL. \(^6\)-\(^8\) Miltefosine has been considered a safe drug with uncommon adverse reaction usually including gastrointestinal symptoms.\(^9\),\(^10\) However, recent reports from Indian and other Asian subcontinents has revealed a serious corneal complication with miltefosine.\(^11\)-\(^14\) Keratitis have consistently been demonstrated in these reports. Although these reports have highlighted the occurrence of corneal complications with miltefosine, little is known about the clinical manifestation, course and management of this condition.

**Purpose:**

This study aims to discuss the diagnostic clinical features, progression and management of miltefosine-related keratitis in six consecutive PKDL patients treated in a single institute within two years.

**Patients and methods:** We retrospectively reviewed five PKDL patients presented with keratitis at our cornea clinic at Indira Gandhi Institute of Medical Sciences, Patna (Bihar) between April 2018 and June 2020. All patients had received miltefosine for PKDL at different kala-azar centers of Bihar. Written informed consent was obtained.

The initial evaluation included a thorough medical history, with a focus on management of VL and PKDL including dose and duration of treatment with miltefosine, and onset of keratitis after initiation of the drug. The ophthalmic workup for keratitis included size, location and pattern of corneal lesion,
depth and extent of stromal infiltrate, extent of oedema, evidence of corneal thinning and presence or absence of a hypopyon and epithelial defect. Intraocular pressure and assessment of visual function were also noted.

All patients underwent corneal scraping under aseptic conditions for detailed microbiological work-up. Additionally, corneal scraping or corneal button and skin biopsy were subjected to Quantitative PCR (qPCR) and Leishman-Donovan (LD) body examination. The rK 39 rapid immunochromatographic rapid diagnostic test and lab parameters were performed in all cases.

Results: All patients were immuno-competent with no history of concomitant systemic illness. They presented with pain, watering, photophobia, diminution of vision. Oral and topical steroid with broad-spectrum antibiotic drops and discontinuation of miltefosine were the mainstay of treatment for all patients in controlling the keratitis. The following are the brief summary of all cases.

Case 1: A 31-year-old male presented with complaints of redness, pain, and photophobia in both eyes for 17 days and had been receiving miltefosine 50 mg twice daily for 48 days. On examination, his BCVA was 20/200 in the right eye and 20/125 in the left eye. Slit-lamp biomicroscopy revealed full thickness paralimbal infiltrate with 3.5 and 1.00 mm hypopyon in right and left eye respectively. The infiltrate progressed centripetally involving almost all cornea resulting into corneal thinning in two days despite being on treatment. The visual acuity dropped to hand movement in right eye and 20/400 in left eye. Penetrating keratoplasty (PK) was performed in right eye.
under peribulbar anesthesia due to impending perforation and rapid progression of ulcer (graft size 8.5 mm). The left eye keratitis was resolved on medical treatment over a period of 5 months. Along with oral corticosteroid, topical prednisolone acetate 1%, topical moxifloxacin 0.5% and cycloplegic eye drops were administered in both eyes, and the patient was kept on a close follow-up with tapering dosage of oral as well as topical steroid over 5 months. A BCVA of 20/80 was achieved in both eyes after 6 months of follow-up.
Case 2: A 45-year-old male sought treatment for ocular symptoms of pain, watering, foreign body sensation, photophobia and diminution of vision in both eyes for 20 days. On examination, his BCVA was 20/125 in the right eye and 20/200 in the left eye. He was initially treated by local physician and was on miltefosine 50 mg twice daily when presented at our center. Slit-lamp biomicroscopy demonstrated a ring-shaped full thickness paralimbal infiltrate (3.0 mm width) in both eyes, rapidly extending towards the center and causing sloughing and thinning of peripheral stroma. Oral and topical
steroid, broad-spectrum antibiotic and lubricant drops were initiated and PK was done owing to impending perforation in right eye. The left eye keratitis resolved completely over a period of 4.5 months leaving a perilimbal corneal opacity. At the end of 6 months of follow-up, a BCVA 20/125 in right eye and 20/40 in left eye was regained.

Bilateral keratitis (case 2). Full thickness paralimbal stromal infiltrate progressed to ulcer with multiple grooves with rapid progression causing peripheral corneal thinning
Case 3: A 16-year-old female patient sought treatment for pain, watering, foreign body sensation, photophobia and diminution of vision in both eyes for 20 days after 38 days of initiation of miltefosine. She showed full thickness corneal infiltrate with overlying epithelial defect of 3.0 mm in greater linear dimension, marked stromal edema and hypopyon of 2.5 mm in right eye. Conjunctival congestion was present in both eyes. Following initiation of topical steroid and antibiotic, hypopyon resolved in 3 weeks while keratitis and adjacent edema showed complete healing at the end of 3 months and attained BCVA of 20/20.
Case 4: A 30-years-old female patient presented after 3 days of appearance of ocular symptoms. Slit-lamp biomicroscopy revealed a paralimbal annular stromal infiltrate with an intervening clear zone (lucid interval) to the limbus. The lesion was associated with adjacent marked stromal edema and Descemet membrane folds but no evidence of overlying epithelial defect. After receiving topical steroid and antibiotic, she achieved a vision of 20/20 over a 2.5 months period.

Unilateral keratitis (case 3). Full thickness juxtalimbal infiltrate with overlying epithelial defect, hypopyon and dense stromal haziness in right eye

Unilateral keratitis (case 4). A ring-shaped paralimbal infiltrate with the presence of lucid interval (black arrow) in the right eye
Case 5: A 28-year-old male patient presented with congested conjunctiva in both eyes and full thickness annular corneal stromal infiltrate with marked edema and no epithelial defect in right eye. The lesion worsened with appearance of an epithelial defect of 8.0 mm in greater linear dimension over 2 days after presentation due to delayed initiation of steroids. Complete resolution of corneal signs and correction of vision (20/20) was achieved over a 3-month period on initiation of topical steroids.
Discussion:

Miltefosine, a phosphocholine analogue originally developed as an antimalignant drug, has been recommended by WHO as the only oral agent to treat all types of leishmaniasis since 2002.\(^{15}\) It is an inhibitor of Akt or protein kinase B which is a crucial protein involved in cell survival.\(^ {16}\) The current guidelines suggest that all PKDL cases should be treated with miltefosine for 12 weeks; the recommended initial dose is 100 mg/day for patients with a body weight >25 kg, and 50 mg/day for body weights <25 kg.

Keratitis as a complication of miltefosine was first reported by Pradhan et al
in 2018 in two male patients; the manifestations included dense corneal infiltrate on the temporal or superotemporal side extending for 4-5 clock hours accompanied by focal or diffuse congestion. In the same year, keratitis was reported in five Bangladeshi male patients who were taking this drug for PKDL; these patients had conjunctival congestion, 360° peripheral corneal infiltrate and ulceration extending towards center. These lesions were presumed to be Mooren's ulcer or Marginal keratitis. Besides, Hossain MS et al from Bangladesh documented four cases of miltefosine-induced ophthalmic complications in form of annular corneal and Mooren's ulcer. Curiously, a recent report from Bihar has documented occurrence of acute scleritis as well as corneal infiltration in their all four patients taking miltefosine.

In our series, we described keratitis in six PKDL patients receiving miltefosine with characteristic clinical features. Ocular manifestation included pain, foreign body sensation, severe photophobia, and marked diminution of vision along with paralimbal dense full thickness stromal greyish white ring infiltrates progressing centripetal with underlying moderate to severe stromal edema and hypopyon of mean height 1.6 mm (range, 1.00 to 3.5 mm). The BCVA at presentation ranged from hand movement to 20/125. Two cases had bilateral (4 eyes) and four had unilateral (4 eyes) involvement of cornea. Although majority of the previously reported cases were unilateral, we found bilateral involvement in two of our six patients.

The study showed a consistent pattern of keratitis that can be divided into two distinct stages: early and advanced stage. The early stages of keratitis...
are characterized by the ring or annular peripheral infiltrates that tends to involve the juxta limbal cornea with sparing center and limbus. Another characteristic features of early stage disease were full thickness stromal infiltrates with preserved corneal sensation and the presence of intervening clear zone (lucid interval) to the limbus with minimal or no epithelial defect. However, as the disease advanced it extended both centripetally and circumferentially to involve the center and limbus. The ring lesion evolved into an ulcerative keratitis that formed multiple concentric grooves caused by corneal melting and thinning, and gave an impression of impending perforation.

Discontinuation of the offending agent and initiation of corticosteroids therapy are the key steps in management. The unilateral cases have excellent outcome with topical steroids, but poor outcomes can be anticipated in patients with bilateral disease. Out of 8 eyes, 4 with unilateral disease responded well to topical steroid. However, eyes with bilateral keratitis required oral steroids and also longer time to heal. In addition, risk of perforation due to corneal thinning prompted us to perform PK in 2 eyes from bilateral cases. We believe that continued miltefosine treatment in presence of early sign of disease in one eye was the main reason why the bilateral cases had severe keratitis or poorer outcome. Thus, based on the results of this study, we can suggest that effective management of miltefosine-related keratitis should follow four steps: (1) stopping the miltefosine, (2) excluding infectious etiology, (3) initiating early anti-inflammatory therapy with steroids and (4) deferring penetrating keratoplasty for the complicated cases.
Conclusion:

Miltefosine when given for prolonged periods in PKDL patients can cause keratitis that resembles infectious keratitis. Early diagnosis with discontinuation of the drug is the key of management. Topical steroids are effective in early and unilateral keratitis. However, advanced and bilateral keratitis have poor outcome and may require PK.

References:


2018; 17;12: e0006781.


This paper was judged as the BEST PAPER of Cornea - II

DR. PINKAL SHIROYA

TO ANALYSES THE LONG-TERM OUTCOME OF DEEP ANTERIOR LAMELLAR KERATOPLASTY IN PEDIATRIC KERATOCONUS.

Abstract

Aim and objective

To analyses the long-term outcome of deep anterior lamellar keratoplasty in pediatric keratoconus.

Method and materials

This is retrospective study of patients less than 18 years who underwent deep anterior lamellar keratoplasty (DALK) for keratoconus from February 2008 to December 2019. Data included preoperative ophthalmic evaluation was done. The outcomes measures included were best corrected visual acuity, mean keratometry values, epithelial defect healing time and surgical/post-operative complications.

Results:

227 eyes of 186 patients were included. The mean uncorrected visual acuity (UCVA) and best spectacle corrected visual acuity (BSCVA) improved to
0.51±0.39 and 0.49±0.33 LogMAR units (p<0.001) respectively. The mean keratometry was 51.51± 5.82D postoperatively. The epithelial healing time was 4.25+6.23 days. Suture removal was initiated at 7.81±7.66 months and completed by 29.26±19.70 months. The complication encountered were Descemet membrane (DM) perforation 15.39%, double anterior chamber 3 cases, vascularization in 13.2%, secondary glaucoma in 14.9%, cataract in 5.7%, graft infections in 9.3%, graft rejection in 6.6% and graft melt in 1.3%.

**Conclusion**

DALK although challenging in pediatric cornea; provides good optical & refractive outcome with long-term graft survival.

**Introduction:**

Keratoconus an ectatic corneal disease characterized by progressive stromal thinning, irregular astigmatism and defective vision. It starts at puberty and progress rapidly to an advanced stage. It poses a burden to society as it affects quality of life, social and educational development. Hence early diagnosis, recognition of progression and timely intervention with measures such as collagen cross-linking or keratoplasty is required. Severe ocular allergy when associated also hastens progression. Studies on pediatric keratoconus suggest that at the time of diagnosis, 22.8% present in an advanced stage of the disease and 88% progress. In children keratoplasty can be challenging due to lower scleral rigidity, the need for recurrent general anesthesia, the tendency for early suture related problems, infections and graft rejection due to a stronger immune system. Deep Anterior Lamellar Keratoplasty (DALK) has become the preferred procedure.
for keratoconus since it retains structural integrity and reduces the chance of endothelial rejection. However, the procedure is technically complex even in adult corneas. This study analyses the feasibility of DALK in pediatric keratoconus, long term visual and functional outcomes and complications.

**Methods**

This is a retrospective analysis of an interventional case series. Informed consent was obtained from patients as well as from Institutional Review Board to review and share the data. Medical records of all keratoconus patients less than 18 years of age who underwent DALK for keratoconus were analyzed. Preoperative corneal status by slit-lamp examination, topography and visual status by uncorrected and best-corrected visual acuity (UCVA, BCVA), presence of local or systemic comorbidities were noted.

Keratoplasty, preferably DALK was planned in children with advanced keratoconus, with inadequate best-corrected spectacle visual acuity.

Penetrating keratoplasty was done mostly for post hydrops corneas. All surgeries were done under general anesthesia. Big bubble technique was attempted in all eyes. If it failed, the procedure was completed with either manual layer-by-layer dissection or hydro-dissection. A 0.25 mm oversized donor button was sutured with a minimum of 16 interrupted sutures with 10-0 nylon. Post-operatively topical antibiotics were given for 2 weeks, prednisolone acetate started four times and gradually tapered to one time daily by 6 months. It was replaced by loteprednol by 12 months or earlier in steroid responders. Cyclosporine A 0.1% was also added and continued. If
the sutures became loose before 3 months, they were replaced as per wound integrity. Suture removal was done in batches by around 12 months if the graft-host junction scar was dense enough. Surgical details like the achievement of big bubble, need for manual or hydrodissection were noted. Incidence of Descemet’s membrane perforation and whether it was converted to penetrating keratoplasty were also noted. Post-operatively problems in wound healing including epithelial healing, early loosening of sutures, need for pneumo-pexy for detached Descemet’s membrane, time to start and end of suture removal, stable refraction and visual acuity was noted. Complications like glaucoma and its management, vascularization, infection, graft rejection and their outcomes were also analyzed.

Results

227 eyes of 186 patients who underwent DALK for keratoconus from February 2008 to December 2019 were evaluated retrospectively. The mean age group was 14.87±2.68 (range 6 to 18 years). 70.5% (n=160) eyes were males and 29.5% (n=67) were females, 50.7% (n=115) were right eyes and 49.3% (n=112) were left eyes. On examination 35.7% (n=81) eye had scar on preop evaluation and 1.3% (n=3) had deep scars on anterior segment optical coherence tomography (ASOCT). Vernal keratoconjunctivitis (VVK) was seen in 39.2% of eyes (n=89). Patients were followed up for a period of 47.63 ± 31.66 months eyes (range 2-130 months). The preoperative UCVA was 1.27±0.27 logmar units (n=227), preoperative BSCVA was 0.67±0.31 and best-corrected contact lens acuity was 0.24±0.26 (n=181). Postoperative UCVA was 0.76±0.29 logmar units (n=225) and BSCVA was
0.18±0.16 (n=222). On comparision, the UCVA showed a significant improvement of 0.51±0.39 logmar units (p<0.001), and the BSCVA also showed a significant increase by 0.49±0.33 logmar units (p<0.001).

The preoperative refraction showed an average spherical value of 8.49 ± 5.68D and cylindrical value of 4.97 ± 1.63D. Preoperative topography showed a mean maximum keratometry (Kmax) of 62.67 ± 7.78D (min=43.20 and max=97.80), and simulated keratometry (Sim k) had a mean of -7.76 ± 3.43D. Postoperative period refraction showed a mean spherical value of -2.93 ± 1.80D and cylinder of -2.78 ± 2.17D. Postoperative topography had Kmax of 51.51±5.82D and Sim k of 4.88 ± 2.86D.

On comparing, the mean pre and post-surgical values using T-test, significant decrease in mean spherical power by 5.17±5.29D (p<0.001) and mean cylindrical power by 2.37 ± 2.64D (p <0.001) was noted. Topography also showed a significant decrease in mean K max by 9.56 ± 8.19D (p<0.001) and Sim K by 3.35 ± 4.86D (p<0.001).

Coming to the surgical technique of DALK, in majority of cases big bubble was achieved (66.1%; n=150), manual dissection was done in 21.6% (n=49) and hydro dissection in 11.9% (n=27). Intraoperatively 15% (n=34) of cases had perforation and 11% (n=25) required rebubbling.

The time required for the epithelial defect to heal was 4.25 ± 6.23 days. Suture replacement following DALK was required in 21.6% (n=49) and was done within a mean period of 3.87 ± 2.54 weeks.

Suture removal following surgery was initiated at a mean period of 7.81 ± 7.66 months (n=203) and was completed within a mean period of 29.26 ±
Complications in the post-operative period: vascularisation was seen in 13.2% (n=30), graft infections in 9.3% (n=21), graft rejection in 6.6% (n=15), graft melt in 1.3% (n=3) which were managed conservatively. Glaucoma was noted in 29.5% (n=67) out of these 46.26% (n=31) required anti-glaucoma medication and 4.4% (n=3) required selective laser trabeculoplasty. Evaluating the contralateral eye of these patients, 49.8% (n=113) cases underwent corneal collagen cross linkage, 11% (n=25) underwent DALK & 2.57% (n=6) cases were converted to penetrating keratoplasty.

**Subgroup Analysis of Complications**

**Rejection:**
Most cases were stromal rejection. The mean duration of rejection incidence was 13.38 ± 7.68 months.

**Infection:**
Most cases were suture infiltrate. The commonest organism cultured was Steptococcus. *pneumonia*. One case had a recurrence of shield ulcer with infiltrate. Cases included patients with Down’s syndrome as comorbidity.

**Cataract:**
13(5.7%) cases developed cataract during follow the up period. The most common type was posterior subcapsular cataract. 3 patients underwent cataract surgery during follow up. 3/13 cases (23.08% among those developing cataracts) had Descemet’s perforation at the time of surgery, out
of which 2 cases (15% among those developing cataracts) required rebubbling in the postoperative period.

Suture Replacement: 49 cases required replacement in the immediate postoperative period. 18/49 cases had vernal keratoconjunctivitis as comorbidity. Among the keratoconus patients with VKC undergoing DALK 20.22% will require early suture replacement.

Miscellaneous:

3 cases developed intact DM detachment and required intracameral air injection. One eye developed Urrets Zavalia syndrome after pneumopexy. Three cases of non-healing epithelial defect required chemical tarsoraphy by botox injection, and one of these also required amniotic membrane graft.

Discussion

Pediatric keratoconus is associated with good visual recovery as well as graft survival among other congenital or acquired traumatic indications after keratoplasty. Penetrating keratoplasty in children is reported to be challenging due to anatomical factors like lower rigidity, narrower palpebral fissure and crowded anterior segment. Moreover, endothelial rejection which can lead to graft failure is expected more in children due to a stronger immune system. Most of the studies on keratoplasty in children analyze both penetrating keratoplasty and DALK for mixed indications. Our study reports the safety of doing DALK exclusively in pediatric keratoconus and its short- and long-term results. Deep Anterior Lamellar Keratoplasty preferred over full thickness in adults too as it preserves anatomical stability as well as eliminates endothelial rejection. Aurora et al reported 80% of big bubble
achievement and Feizi et al showed 75% achievement which is much more as compared to our study with 66 % achievement perhaps because of varying levels of experience among the surgeons. Elbaz et al suggested manual dissection as a safe method in children to avoid conversion to penetrating keratoplasty. Though DM perforation was noted in 15% of cases, we could complete the procedure in all but 3 cases of post hydrops corneas. Feizi et al reported the visual acuity was comparable between big-bubble and manual dissection in pediatric as well as in adult keratoconus. Patel et al reported BCVA in 86% after PK and Felzi reported in 84% post DALK. We noticed a significant improvement in both UCVA and BSCVA as well as topographic parameters.

The post-operative double anterior chamber was noted in 11%, even with intact DM in 3 cases. All these cases were resolved with pneumopexy, with one eye developing Urrets Zavalia syndrome.

Javadi and Han et al reported immune graft rejection to be higher in post-penetrating keratoplasty than after DALK for keratoconus, in adults. Moreover, in our report, graft rejection was sub-epithelial or stromal in 6.6 %, sparing endothelium, with good recovery. Whereas Javadi et al, Feizi et al reported this as 9.1 – 23.8 %.

Glaucoma was seen in 29 % of our cases, which is higher than the reported 13 - 18% by Feizi et al. Though it was controlled by medication in most of the cases, 4.4% needed intervention in the form of selective laser trabeculoplasty.

Arora et al, Feizi et al, also noted early suture loosening and replacement,
suture tract vascularization, suture infections. In our study vernal keratoconjunctivitis as a comorbidity was associated with delayed epithelial healing, vascularization affecting overall graft survival. VKC with shield ulcer was noted in our study, plaque removal and early initiation of steroids preserved graft clarity in these cases. Similar cases & interventions were adapted by Arora et al.

Cataract was noted in 5.7% of eyes, predominantly posterior subcapsular. Cataract in our study was less than 14 – 25% reported by Javedi et al in ost DALK adults with keratoconus.

**Limitations of the study:**

This is a retrospective analysis with the attendant shortcomings in the availability of some data. We have included cases with follow-ups as early as 2 months to as late as 130 months. However, we wanted to show the possibility of early postoperative problems, which are expected more in children as well as long-term outcomes.

**Conclusion**

Our analysis showed that DALK can be performed safely in pediatric keratoconus, with good visual recovery and graft survival. DALK can be associated with unique technique related complications like DM perforation and double anterior chamber which need to be addressed in time. Vernal kerato-conjunctivitis is a co-morbidity that can be associated with healing and suture related. These children need to be closely monitored for complications like glaucoma and cataract also.
### TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRE UCVA</td>
<td>221</td>
<td>1.275</td>
<td>0.269</td>
<td>0.018</td>
</tr>
<tr>
<td>POST UCVA</td>
<td>219</td>
<td>0.760</td>
<td>0.299</td>
<td>0.020</td>
</tr>
<tr>
<td>PRE BCSVA</td>
<td>219</td>
<td>0.675</td>
<td>0.312</td>
<td>0.021</td>
</tr>
<tr>
<td>POST BCVA</td>
<td>216</td>
<td>0.183</td>
<td>0.160</td>
<td>0.011</td>
</tr>
</tbody>
</table>

### TABLE 2

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRE SPH</td>
<td>150</td>
<td>-8.643</td>
<td>5.701</td>
<td>0.465</td>
</tr>
<tr>
<td>POST SPH</td>
<td>135</td>
<td>-2.917</td>
<td>1.841</td>
<td>0.158</td>
</tr>
<tr>
<td>PRE_CYLN</td>
<td>200</td>
<td>-4.959</td>
<td>1.598</td>
<td>0.113</td>
</tr>
<tr>
<td>POST CYLN</td>
<td>140</td>
<td>-2.775</td>
<td>2.181</td>
<td>0.184</td>
</tr>
</tbody>
</table>

### TABLE 3

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRE KMAX</td>
<td>149</td>
<td>62.654</td>
<td>7.738</td>
<td>0.634</td>
</tr>
<tr>
<td>POST KMAX</td>
<td>106</td>
<td>51.501</td>
<td>5.852</td>
<td>0.568</td>
</tr>
<tr>
<td>PRE_SIMK</td>
<td>146</td>
<td>7.719</td>
<td>3.447</td>
<td>0.285</td>
</tr>
<tr>
<td>POST SIMK</td>
<td>104</td>
<td>4.897</td>
<td>2.888</td>
<td>0.283</td>
</tr>
</tbody>
</table>

References:


18. Ardjomand N, Hau S, McAlister JC et al. Quality of vision and graft


This paper was judged as the BEST PAPER of Cornea – III

**Dr. Sohini Mandal**

Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India- 110029

**COMPARATIVE ANALYSIS OF POSTERIOR CORNEA BETWEEN HYDROPS IN KERATOCONUS AND HAAB'S STRIAE IN PCG**

**Abstract**

**Aim:**

To compare the morphological characteristics of Descemet membrane (DM) tears in eyes with primary congenital glaucoma (PCG) and keratoconus (KC) using high-definition anterior segment optical coherence tomography (ASOCT) and histopathology.

**Methods:**

ASOCT of PCG eyes with Haab’s striae (15 eyes of 15 patients) and KC eyes with hydrops (12 eyes of 12 patients) were evaluated prospectively for Descemet’s membrane-Pre-Descemet’s layer (DM-PDL) morphology. These features were further assessed retrospectively on histopathology of corneal buttons obtained from 13 PCG and 14 KC eyes after penetrating keratoplasty and compared with 6 retinoblastoma eyes on light microscopy and immunostaining for Collagen IV.
Results: ASOCT showed significantly thicker DM-PDL in PCG (77.2 ± 26.2 μm) than that of KC eyes (47.1 ± 25.5 μm) (p<0.01). Both groups showed hyper-reflective double layer. On the contrary, histopathology showed thicker DM-PDL in KC eyes (91.7±77.5 μm) than that of PCG eyes (62.5±57.3 μm) (p<0.01). PCG eyes have generalised thickening of DM and PDL in response to high IOP, more so in areas of Haab’s striae which heal by localised hyper-proliferation. On the contrary, keratoconus eyes with hydrops have higher posterior corneal thickening in areas of rupture which don’t act to seal the break but result in retraction and coiling of DM/PDL.

Conclusion:

This differential response of the posterior cornea may be responsible for the varied clinical presentation of the DM tears between the two groups.

Keywords:

Descemet’s tear, DM-PDL complex, Haab’s striae, corneal hydrops, primary congenital glaucoma, keratoconus.

Introduction

The response of corneal tissue to Descemet’s membrane (DM) tears in two different diseases of primary congenital glaucoma (PCG) and keratoconus is distinctly different. Contrary to PCG, acute corneal hydrops in cases of advanced keratoconus, is associated with stretching and rupture of DM, resulting in transient corneal edema and intrastromal fluid clefts.(1) However, recently Parker et al in their study proved that a defect at the level of DM is not sufficient to elicit an acute corneal hydrops, unless also
accompanied by a defect in the posterior corneal stroma. (2) PDL possesses special mechanical properties that includes high tensile strength, impermeability to air, and a distinctive collagen makeup featuring a greater amount of type VI collagen and longer spacing fibrils. Cherif and associates demonstrated that compression sutures placed in the deep posterior stroma may be an effective treatment for corneal hydrops and theorized that posterior stromal breaks were the root cause of the condition. (3) Hence, both these studies point towards the fact that the DM tears alone may not be sufficient to induce hydrops in keratoconus eyes and PDL tears may also be a necessary pre-requisite for inducing the breaks. Although the prevalence of an episode of corneal hydrops in clinic-based patients with keratoconus has been estimated to be between 2.6 and 2.8%. (4,5)

The differential responses of PCG and keratoconus to the corneal tears, is the subject of intrigue for us. While corneal tears in PCG induce Haab’s striae with resultant corneal edema which often resolves on lowering of IOP if done in time, tears in keratoconus induces corneal hydrops with poor resolution rates. The hypothesis leading to the study is that whether the rapid endothelial regeneration in children eyes in tandem with a thickened PDL act concurrently to prevent stromal edema to ensue and to last to some extent in these cases. This led us to envisage this study to assess the morphological characteristics of DM and PDL both in vivo (ASOCT) and on histopathology and to explore possible differences between the PCG and keratoconus eyes, especially in areas with Haab’s striae.

**Methods**
**ASOCT Study**

The prospective study included two groups, one of which had confirmed cases of advanced keratoconus with corneal hydrops (acute and healed) and the other had confirmed cases of primary congenital glaucoma (PCG) who had undergone a single surgery (trabeculectomy and trabeculotomy). All the patients were old enough (>8 years) to cooperate for a slit-lamp mounted ASOCT examination and gonioscopy. Cases of corneal hydrops with vision of at-least finger counting at 1 meter, were compared with those of unilateral/bilateral PCG with enlarged corneal diameter (>12 mm). All patients underwent a complete ocular examination including uncorrected distance visual acuity (logMAR), corrected distance visual acuity (logMAR), intraocular pressure (mmHg) and refractive error (spherical equivalent). At slit-lamp examination, corneal diameter (mm), corneal clarity (clear/ mild haze with visible iris details/ moderate haze with slightly visible iris details/ severe haze with absence of iris details), location of hydrops/ Haab’s striae (central/ peripheral/ both) and extent of Descemet’s membrane tear (clock hours) were noted.

Any other form of primary corneal ectatic disorder such as pellucid marginal degeneration, keratoglobus, posterior keratoconus, and previous history of corneal collagen crosslinking or keratoplasty procedure were excluded in the keratoconus group. Similarly, PCG eyes with isolated trabeculodysgenesis were included, whereas those having evidence of any other ocular comorbidity like prominent Schwalbe line, angle recession, angle pigmentation ≥ grade 3, peripheral anterior synechiae, nystagmus, poor fixation, microcornea, corectopia, ectropion uveae, cataract, Peter...
syndrome, aniridia, or a history of steroid use were excluded.

The study was conducted after approval from Institutional Ethics Committee and was carried out in accordance with the tenets of Declaration of Helsinki. Written and informed consent was obtained from all patients/parents before inclusion in the study. All study patients underwent clinical photography of the anterior segment with additional goniophotography for PCG patients on Eye Cap (Haag-Streit International, Koniz, Switzerland).

High resolution in vivo ASOCT (Spectralis, Software version 6.5; Heidelberg Engineering GmbH, Heidelberg, Germany) was performed twice for all study patients, 2 weeks apart by two different examiners using an anterior segment lens to assess the cornea. This was done to ensure reproducibility and an average of the 2 readings was taken for analysis. Corneal scans from central, mid peripheral, and peripheral cornea were taken on “high resolution anterior segment module” for scanning DM and PDL. For the purpose of this study, horizontal cross-sectional scans through 3- and 9-o’clock meridians were used for analysis. If these were marred by the presence of the Haab striae or hydrops, scans from adjacent horizontal meridians were considered. The ASOCT manual caliper tool was used to measure the DM thickness at 3 points in central 6-mm cornea (avoiding the areas with Haab striae and hydrops), zoomed at 400% for ease in identification, and an average of the 3 readings was taken for analysis. The 3 random points chosen were such that 2 were at the periphery of the chosen section and one at the centre while making sure that the caliper was kept perpendicular to the endothelium.
Initial medical management of acute hydrops was done with topical 5% sodium chloride 6 times, 1% prednisolone phosphate 6 times, 0.5% moxifloxacin 3 times, 0.5% timolol 2 times, homatropine 2% 2 times and lubricants 4 times a day. Intracameral perfluoropropane (14% C3F8) injection with or without supra-descemetic fluid drainage was performed preferably on the same day of presentation.

**Statistical Analysis**

Data were entered in Microsoft Excel and analysed using Stata 12.0 software (StataCorp LP, College Station, TX). Data were presented as number (%) or mean ± SD as appropriate. A 2-sample t test was calculated to derive the difference between the two ASOCT study groups. A Mann-Whitney U test was used for data that did not have a normal distribution. A p value <0.05 was considered statistically significant.

**Results**

**ASOCT Study:** Twelve eyes of 12 keratoconus patients and fifteen eyes of 15 PCG patients were analysed on ASOCT. The mean age of the patients with keratoconus at the time of OCT examination was 21.2 ± 6.4 years (range 14-36 years) whereas that of PCG was 16.1 ± 4.9 years (9-25 years) (p<0.001). The disease duration was significantly higher in KC eyes (21.2 ± 6.4 years) than that of the PCG eyes (14.8 ± 8.1 years). The mean highest baseline IOP documented was 15.43 ± 2.59 mm Hg and 31.81 ± 6.11 mm Hg in the keratoconus and PCG group respectively. The mean spherical equivalent was -5.50±4.81 DS (-14.00 to -2.25 DS) and -3.25±4.78 DS (-10.00 to +3.00 DS) in keratoconus and PCG group respectively. The mean keratometry and corneal...
astigmatism was significantly higher in the KC group (56.1 ± 11.5 D and 6.00 ± 5.50 DC). The mean horizontal corneal diameter was 11.93 ± 0.39 mm and 13.61 ± 0.86 mm in keratoconus and PCG eyes respectively. 66.7% of PCG eyes and 41.7% of KC eyes undergoing ASOCT presented with clear cornea. Mild to moderate to severe corneal haze was present in the remaining eyes. ASOCT revealed significantly thinner corneas in the KC group (394.8 ± 70.1 μm) in comparison to the PCG group (526.7 ± 56.5 μm). Additionally, ASOCT also showed significantly thinner DM-PDL complex inside (47.1 ± 25.5 μm) the areas of hydrops in keratoconus group when compared to the PCG group (77.2 ± 26.2 μm) (p<0.01). Similar findings were noted outside the areas of hydrops (15.6 ± 4.3 μm) in keratoconus group in comparison to the PCG group (20.4 ± 5.5 μm) (p<0.01). Both the groups showed the DM-PDL complex as two separate hyper-reflective lines with translucent space in between, giving it a “double membrane” appearance.

The DM was found to be globally thickened in all scans of PCG eyes with intracameral protuberances of varying sizes and shapes in the areas of Haab’s striae.

**Discussion**

Because PCG and keratoconus needs lifelong therapy, follow-up and visual rehabilitative measures, understanding the corneal pathology is equally important for the clinicians, which needs to be accounted for. This comparative study showed thickening of DM in PCG eyes in vivo on ASOCT. DM is instrumental in maintaining the morphology and function of corneal endothelial cells under physiological conditions. Increased DM thickness in
PCG eyes when compared to KC eyes, as seen in our study, may be attributed to the fibrotic proliferative response that ensues following DM tears during corneal stretching as has been postulated in previous study by Gupta et al. (4) DM tears may present in association with transient corneal edema, corneal decompensation, or even with a clear cornea once the gap is sealed by regenerating endothelium. Tears in DM stimulate the endothelial cells to migrate and seal the gap through normal wound healing process. Chen et al, in a rabbit model of endothelial cell injuring vivo, showed that there was intracorneal fibrous tissue formation in the group that underwent DM stripping along with injury to the endothelial cells; this fibrotic response was absent in eyes with endothelial cell injury alone but with intact DM. Most of the cells in the posterior fibrotic tissue did not originate from endothelium. (5,6) As DM ruptures, its edges have been shown to curl inside and entrap keratocytes in contact with the corneal stroma and advancing endothelial cells, stimulating a proliferative response eventually sealing the DM break with deposition of new material. (7) This DM thickening response to injury, as seen in PCG eyes, is not observed in eyes with keratoconus with DM tears. In our PCG cases, the DM was not wavy or irregular except in areas overlying the Haab striae where there were focal protuberances on ASOCT. However, the PDL could be appreciated as a thickened layer on both ASOCT and H&E staining.

Cherif et al had demonstrated that compression sutures placed in the deep posterior stroma, apparently to repair the PDL breaks in eyes with hydrops with keratoconus, may be an effective treatment for resolution of corneal edema. This is further supported by observations of Parker et al, who
showed that in eyes with keratoconus, contrary to what is widely believed, DM breaks may not alone suffice for the development of acute hydrops and that additional discontinuity in PDL is imperative for this complication to set in. They showed that intraoperatively those eyes which underwent Bowman layer transplant in cases with advanced keratoconus developed corneal edema because of injury to PDL, unlike in eyes which underwent endothelial keratoplasty alone with intact PDL.(2,3)

One of the limitations of our study was that our patient cohort had been operated in the past. Moreover, eyes in the histopathological arm of the study having undergone keratoplasty might represent a more severe form of corneal involvement compared with those which retained a clear cornea at the time of imaging. This was apparent from the greater DM thickness that we observed from the histopathological samples of keratoconus eyes in comparison to in vivo imaging. One of the strengths of our study is the comprisal of a large cohort of well characterized PCG eyes where children were old enough to undergo an ASOCT evaluation. Owing to the retinoblastoma controls being younger in age at the time of surgery, the age matching of cases and controls in the histopathological arm was not possible.
References


TARGETED LASER PHOTOCOAGULATION OF RIM ANEURYSMS IN DIABETIC MACULAR EDEMA

Abstract

Purpose:

To evaluate the efficacy of targeted laser photocoagulation of rim aneurysms in diabetic macular edema (DME).

Methods: Fundus photograph of cases with DME were screened for presence of larger capillary aneurysms with white rim. Optical coherence tomography (OCT) was used to confirm the presence of rim aneurysms, which is detectable as oval structure with hyper reflective margin and hyporeflective lumen. Targeted laser photocoagulation was performed to achieve complete blanching of rim aneurysm.

Results: Ten cases of DME with rim aneurysm were included in the study. Four cases were previously treated with anti VEGF injections with poor response. The cases were treated by targeted laser photocoagulation.
Complete resolution of macular edema was noted in 6 eyes, partial resolution in 2 eye and no reduction in 2 eyes during follow up. Conclusion: Cases with rim aneurysms respond poorly to anti VEGF injections and targeted photocoagulation is effective in resolution of DME

INTRODUCTION:

Diabetic macular edema (DME) is one of the leading causes of visual impairment in patients with diabetic retinopathy. Leak from microaneurysms and incompetent capillaries results in macular edema. Microaneurysms are usually tiny and measure 25 to 100 micron in size. However, larger aneurysms arising from retinal capillaries are described in diabetic retinopathy and retinal vein occlusions. Macular edema due to larger aneurysms respond poorly to intravitreal anti VEGF therapy.\textsuperscript{1,2} Few studies have noted good response to laser photocoagulation in cases with macular edema secondary to larger aneurysms. Indocyanine green angiography and infrared reflectance image are described to be a better imaging modality in identification of such larger aneurysms.\textsuperscript{2,3} In this series, we describe successful treatment of macular edema with targeted laser photocoagulation in eyes with DME secondary to large aneurysms with rim.

Methodology

This is a retrospective study of eyes with DME secondary to large aneurysms with rim treated with targeted laser photocoagulation from October 2018 to September 2021. Both treatment naïve cases and cases which did not respond to intravitreal pharmacotherapy were included in the study. Best corrected visual acuity (BCVA) was recorded with Snellen’s chart. Color
photograph and optical coherence tomography (OCT) was performed with Topcon DRI OCT Triton. Color photographs were screened for the presence of large aneurysms with rim within in the edematous area of macula. Optical coherence tomography (3D macula protocol) was used to confirm the presence of aneurysm. Aneurysm was seen as a vertically oval structure with hyporeflective lumen and hyper reflective margin. Laser photocoagulation was performed with double frequency Nd:YAG slit lamp indirect delivery. Cases were followed up monthly. BCVA, Color photograph and OCT was recorded at each visit. If the edema was persistent at 3 months, alternate treatment options were recommended. Cases with follow up of at least 3 months were included.

Results

Ten eyes with centre involving DME were included in the study. Six cases were treatment naïve and four cases were previously treated with intravitreal pharmacotherapy with poor response. Six eyes showed complete resolution of macular edema, 2 cases showed partial resolution and 2 cases did not show any signs of reduction by 3 months. Nine of the 10 eyes showed complete occlusion of aneurysm by 3 months. Improvement in visual acuity was seen in all the 6 cases that showed complete resolution of macular edema.

Discussion

Larger aneurysms arising from the capillaries are seen in eyes with DME. It has been described that macular edema secondary to such larger aneurysms do not respond well to intravitreal therapy which results in chronic edema.
and progressive vision loss. In our study we noted that targeted laser photocoagulation results in occlusion of such aneurysms in most of the cases. Anatomical improvement in terms of resolution of macular edema was seen in 60% of cases. Visual improvement was also seen in 60% of cases. The limitations of the study are retrospective nature of the study, small sample size, variable follow up period. Confounding factors such as glycemic control were not considered.

Reference:


MECHANOTRANSDUCTION: A PARADIGM SHIFT IN THE PATHOGENESIS OF AGE-RELATED MACULAR DEGENERATION

Introduction:

GA (expand GA) is characterized initially by sub-RPE (expand) deposits that accumulate between the RPE and the Bruch's membrane (BM). The last three decades of AMD (expand) research have been primarily focused on identifying the biochemical components of these sub-RPE deposits and targeting individual components of these deposits has been the predominant treatment strategy. However, these strategies thus far, have been a futile endeavor as evidenced by multiple clinical trials. Despite being the pathological hallmarks of GA and AMD (expand), the effect of the mechanical changes caused by these deposits on RPE homeostasis has not been studied. Mechanotransduction, a phenomenon governing the fates and functions of biological systems by mechanical forces, has been found to occur in all corners of the biological realm with an extensive and diverse repertoire of
mechanisms. In exciting, new preliminary studies, we observed a role for mechanotransduction in RPE homeostasis and degeneration in GA. Hence, although inflammation is considered to be the primary process by which RPE cell death occurs in GA, we hypothesize that while RPE degeneration is perpetuated by inflammatory mediators, it is initiated by mechanical factors.

Methods:

Human tissue:

Doner eyes from patients with GA due to AMD and normal age-matched control were obtained from various eye banks. The diagnoses (diagnosis) were confirmed by both the medical history and post mortem examination. The study followed the guidelines of the Declaration of Helsinki.

Mice:

All animal experiments were performed in accordance with the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Visual Research. Mice between 6-8 wks. were used. Wild-type C57BL/6j, Best1-Cre, TAZ f/f, YAP/TAZ f/f mice were obtained from the Jackson laboratory. YAP f/f mice were bred from YAP/TAZ f/f mice. For all procedures, anesthesia was achieved by intraperitoneal injection of 100 mg/kg ketamine hydrochloride (Ft. Dodge Animal Health) and 10 mg/kg xylazine (Phoenix Scientific), and pupils were dilated with topical 1% tropicamide (Alcon Laboratories) and 2.5% phenylephrine (Alcon Laboratories).

Subretinal injection:
Subretinal injections (SRI) were performed in mice using a 35-gauge needle (Ito Co. Fuji, Japan) as described earlier. AAV1-BEST1-Cre or AAV1-BEST1-GFP were injected at 1.0x10^11 using a in Yapf/f, Tazf/f, Yap/Taz f/f mice or wild-type mice.

Fundus photography:
Photos of mice fundus were acquired by TRC-50 IX camera (Topcon) linked to a digital imaging system (Sony).

Assessment of RPE degeneration:
Seven or fourteen days after SRI, RPE health was assessed by fundus photography and immunostaining of the zonula occludens-1 (ZO-1) on RPE amount described before. Briefly, mouse RPE and choroidal flat mounts were fixed with 2% paraformaldehyde, stained with rabbit polyclonal antibodies against mouse ZO-1 and Alexa Fluor 594 conjugate (1:100, Fisher). RPE degeneration quantification was assessed by three masked graders.

Histology:
Hematoxylin and eosin staining were performed as described before []. Briefly, mice eyes were collected and embedded in Optimal Cutting Temperature Compound (Fisher) and frozen in precooled isopentane by liquid nitrogen. Cryosectioned slices at 10 um thickness were stained using the H&E Frozen section staining kit (Thermo scientific).

Cell culture:
Cell lines were cultured at 37 C and 5% CO2. Primary mouse RPE cells were
isolated as previously described and grown in Dulbecco’s modified Eagle’s medium (DMEM) supplemented with 10% FBS and standard antibiotics concentrations. Primary human RPE cells were isolated as previously described and maintained in DMEM supplemented with 20% FBS and antibiotics.

**Transient Transfection:**

All siRNA (Silencer select) were purchased from Thermo Fisher. Human or mouse RPE cells were transfected with human Yap siRNA (s20366), mouse Yap (187076), human TAZ siRNA (Thermo Fisher), mouse TAZ siRNA (175678), and negative control (4390843) with Lipofectamine 2000.

**Western blot:**

Cell and tissue lysates prepared in RIPA (expand RIPA) buffer were homogenized by sonication. Protein concentration was determined with a Pierce BCA Protein Assay Kit (Thermo Fisher Scientific). Equal quantities of protein (10–50 μg) prepared in Laemmli buffer were resolved by SDS–PAGE on Novex Tris-glycine gels (Invitrogen) and transferred onto Immobilon-FL PVDF (expand) membranes (Millipore). The transferred membranes were blocked in Odyssey Blocking Buffer (PBS) or 5% nonfat dry skim milk for 1 h at RT and then incubated with primary antibody at 4 °C overnight. The antibodies used were as follows: rabbit anti-GAPDH (expand) (1:1000, cell signaling technology, 2118), mouse anti-TAZ (1:1000, Fisher Scientific, 560235), mouse anti-YAP (1:1000, Santa Cruz Biotechnology, sc-101199), rabbit anti-Yap1 (1:1000, Cell Signaling Technology, 14074).
**Results:**

**YAP/TAZ expression is downregulated in the RPE in GA:**

Western blotting (Figure 1 left, top panel), immunohistochemistry (Figure 1 left, bottom panel) and real-time polymerase chain reaction (Figure 1 right panel) show decreased YAP/TAZ (expand) expression in the RPE of donor eyes with GA.

Figure 1: Western blotting (left, top panel), immunohistochemistry (left, bottom panel) and RT-PCR (right panel) show decreased YAP/TAZ expression in the RPE of donor eyes with GA.

**YAP/TAZ knockdown produces spontaneous RPE degeneration:**

Conditional RPE-specific knockdown of YAP and TAZ expression in the RPE induced spontaneous RPE degeneration.

Figure 2: Fundus photography, optical coherence imaging, histology and ZO-1 staining of RPE flat mounts shows that subretinal injection of AAV2-BEST1-Cre induced RPE degeneration in Yap f/f/Taz f/f mice (bottom panel) but not in C57BL/6J mice (top panel).
TAZ (expand) knockdown produces spontaneous choroidal neovascularization (CNV):

Figure 3: FFA images of Taz f/f mice injected with AAV-Best1 Cre show features characteristic of choroidal neovascularization
Conclusion:

This study provides new evidence to suggest a paradigm shift in our understanding of the pathogenesis of GA (expand) by deciphering a role for the mechanical effects induced by sub-RPE deposits on the RPE thereby identifying potential novel therapeutic strategies.
PLATELET RICH FIBRIN AS 3-DIMENSIONAL STRUCTURAL SCAFFOLD IN SURFACE WOUND HEALING OF EYE AND ORBIT

Introduction

Wound healing and regeneration of local tissue are the elemental objectives of medical science and the orbit is no different in this respect. In this context, one of the considerable challenges of clinical research lies in the evolution of bioactive surgical additives which can aid in not merely countering inflammation but can expedite the healing cascade.\textsuperscript{1} In the face of this challenge, use of autologous blood products has gained some reputation.

The role of platelets in hemostasis is well established, but its role in bone and soft tissue maturation have been extensively researched in the last two decades.\textsuperscript{2} Platelet rich plasma (PRP) enriched with growth factors has been considered a suitable standard for native tissue repair and regeneration as it known to help stimulate mesenchymal stem cell migration and its
differentiation. Platelet rich fibrin (PRF) is a second generation platelet concentrate originally conceptualized for its use in oral and maxillofacial surgery by Choukroun et al. Role of PRF in ophthalmology has recently received a lot of attention. It has been utilized as an adjunct in pterygium surgery, for surgical therapy of refractory macular holes, autologous sealant for exigent salvage of cornea with descemetocoele and in restoring tear film homeostasis in ocular surface disorders. This study aims to establish a similar role of platelet rich fibrin as a three dimensional scaffold with a sustained release of growth factors as a surgical surface adjuvant in the orbit.

Materials and methods:

This was a prospective non-comparative interventional study conducted at the department of Ophthalmic Plastic and Reconstructive Surgery at a tertiary eye care centre. After obtaining clearance from the Institutional Ethics Committee, written informed consent was obtained from all participants after providing detailed explanation of the study design. A total of 14 patients were enrolled who needed reconstruction of eyes and orbit mainly, repair of socket contraction (SC), non-healing lid fistula, wide conjunctival granuloma and lid cicatrix. In addition to the standard surgical protocol for the respective diagnosis of the recruits, PRF was incorporated as a layered surgical adjuvant during closure onto the bare wound.

Preparation of PRF

Whole blood samples were taken from the subjects from the antecubital vein in a 24 gauge needle prior to them undergoing their designated surgical procedure. Samples were collected in 10 ml vacutainers without
anticoagulant and were immediately subjected to centrifugation at 3000 r.p.m. (3000 rotations per minute) for 30 minutes. The fibrin clot synthesized in the middle of the tube was removed and residual blood elements were scraped away. The clot was then compressed to extrude the serum and a PRF membrane was obtained. Once prepared, it was sutured on the wound without any delay using 6.0 polyglactin suture.

Follow up examination

After detailed history of the participants including demographics, medical and ocular history, a comprehensive ophthalmic evaluation of all cases including best corrected visual acuity, tonometry, slit lamp biomicroscopy and dilated fundus examination was performed both before and after surgery. Patients were examined on day 1, at 1 week and then at 4 weeks after surgery. At 4 weeks post operation, the wound was assessed based on the Wound Evaluation Scale (WES) and scored accordingly. In this scale the wound is given scores based on presence of step off borders, contour irregularities, scar width, edge inversion, inflammation and overall cosmesis.

Results:

Wound healing assessment:

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Wound Evaluation Score (WES) at 4 weeks post-op</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>4/6</td>
</tr>
<tr>
<td>12</td>
<td>6/6</td>
</tr>
</tbody>
</table>

After the surgery, patients were called for follow up visits on day 1, week 1.
and at 4 weeks post-operatively. As per the WES, at four weeks, 12 patients had a score of 6 and 2 patients a score of 4. Eight patients of dermis fat graft used for repair of socket contracture showed a WES of 6 at the end of 3.5 weeks.

**Discussion:**

PRF membrane is a three dimensional biodegradable complex succor representing a revolutionary measure in the concept of platelet gel therapeutics. First developed in France by Choukroun et al, this autologous second generation platelet concentrate does not require any gelifying impetus but can be produced by mere centrifugation of the whole blood. It acts as a nidus exuding several growth factors such as fibroblast growth factor (FGF), platelet derived growth factor (PDGF), transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), epithelial cell growth factor and insulin like growth factor (ILGF). It polymerizes naturally and slowly while centrifugation occurs whereas the former bio-actives need agents like bovine thrombin and calcium chloride respectively to commence their process of coagulation. The natural mode offers PRF a condensed tetramolecular structure (bilateral) connected by trimolecular junctions (equilateral). This slower release of growth factors by PRF has been proven via in vitro and in vivo studies to yield better healing outcomes. Additionally injury in the form of a trauma or surgery initiates a cascade recruiting mesenchymal stem cells to the site of compromise. Use of PRF in these sites enmeshes these stem cells and this localization aids in further differentiation. Research has also stated that fibrin acts as a
successful culture medium and a suitable conduit for these mesenchymal stem cells which preserves their paracrine functions conferring them regenerative potential. PRF also has been noted to harbor majority of the leucocytes post centrifugation of the whole blood which itself is a persistent stimulus for reparative homeostatic measures and consequent mesenchymal stem cell entrapment.

Several studies have proven that PRF possesses anti-inflammatory, regenerative, anti-microbial and anti-fibrotic properties similar to amniotic membrane. While the aforementioned is true, PRF also has critical advantages over other grafts utilized for surface reconstruction. It has prompt clinical availability, and being autologous it avoids the risk of viral or prion infections and graft rejection, ensures reproducibility and is economical.

Dermis fat grafting for volume augmentation of contracted socket is the most commonly used autogenous tissue used for reconstruction. Additionally when Dermis fat graft is placed with PRF, it has been noted to improve the microscopic vascular architecture of the graft and also helps to decelerate the fat resorption.

Our initial study employing PRF as a surface adjuvant in cases of ocular and orbital surface reconstruction yielded a positive impression showcasing that PRF membrane functions as an autologous, economical, reproducible, easily available and structurally stable three-dimensional matrix that is a wellspring of elemental growth factors and cytokines triggering regional stem cell differentiation and expedites wound healing cascade.
References:


15. Anitua E, Muruzabal F, de la Fuente M, Riestra A, Merayo-Lloves J, Orive G. PRGF exerts more potent proliferative and anti-inflammatory effects than autologous serum on a cell culture


This paper was judged as the BEST PAPER of Glaucoma - I Session

DR. PRITHVI CHANDRAKANTH
MBBS, MS, FVRS(AEHCBE)
Vitreoretinal surgeon
Department of vitreoretinal services, Aravind Eye Hospital, Coimbatore

SMARTPHONE AND INTRAOCULAR LENS AIDED GONIOSCOPY

Abstract:

Gonioscopy, which is an integral part of glaucoma evaluation, has a steep learning curve. With smartphones revolutionising tele ophthalmology, we present novel method of using smartphone for gonio-imaging. We have previously reported use of smartphone with 10D IOL for anterior segment imaging. In this study we compare use of similar method for gonio-imaging with standard slit lamp imaging. Gonio-images of 120 patients were taken with slit lamp, smartphone and smartphone with attached 10 D IOL and images were graded for quality and diagnosis from 1 to 5 on the basis of Noise, Sharpness, contrast, diagnostic confidence and artefacts by 3 medical officers and were compared. No statistically significant difference was observed between smartphone with 10D IOL and slit-lamp imaging. Conclusion- Smartphone Gonio-imaging has a unique role in glaucoma screening in remote areas along with hand held tonometers. It serves both
as imaging and connectivity device.

Keywords:
Gonioscopy, Smartphone imaging, Gonio-imaging, Anterior chamber angle

Introduction

Glaucoma is the second most common cause of blindness after cataract and the leading cause of irreversible blindness.1 The global prevalence of glaucoma is estimated at 3.54%.2 The studies showing the prevalence of glaucoma between 0.94% to 4.73% among them in various part of Asia, with angle-closure glaucoma being more frequent among Asian populations.3,4 The estimated prevalence of glaucoma cases in India is reported to be 11.9 million with an equal proportion of primary open angle glaucoma (POAG) and primary angle closure glaucoma (PACG). 4 Visual field loss and progressive optic neuropathy in glaucoma are often slow with many patients oblivious to their underlying glaucomatous disease. Population studies in India have proposed periodic screening of high risk populations for diagnosing the disease at an early stage. Imaging the anterior chamber angle via gonioscopy forms an integral part of glaucoma screening, diagnosis and management. Previously anterior chamber angle could be imaged only with slit-lamp based gonio-photography, however recently smartphone based anterior chamber angle imaging techniques have been described.5,6 These techniques utilize an adapter placed on a smartphone camera which is then used to image the anterior chamber angle via a goniolens devoid of a slit lamp. We have previously reported anterior segment imaging using an intraocular lens (IOL) attached to a smartphone camera called anterior
segment photography with intraocular lens (ASPI)7 and in this report we extend as well as describe its use to photograph the anterior chamber angle aided with a goniolens which can be used as a cost effective screening tool.

Methods

This study was conducted in a secondary eye care centre located in an underserved area of South India. The study was conducted according to the tenets of declaration of Helsinki. An ethics committee approval was obtained for this retrospective review. An informed consent was taken from all patients. Patients presenting for a routine ocular exam as well as those suffering from glaucoma were included in the study. A routine ocular examination was performed using a slit lamp. Following anterior segment examination, with the patient in a seated or supine position, topical anesthetic eye drops (Proparacaine HCL, 0.5%, Aurolab, Madurai, India) are instilled in the patient’s eye and a Goldmann 4-mirror goniolens with flanges (Volk Optical Inc., Ohio) is placed over the cornea. Utilizing the smartphone (IOS operating agent- iPhone 5s; Apple, 73 Los Altos, CA) after attaching a 10D IOL over its camera with a micropore and switching on the in-built flash (ASPI) [Figure 1]7 . The image or video of the anterior chamber angle of all quadrants was focused by tapping on the smartphone screen. A highly magnified image was also obtained. Additionally slit images of the anterior chamber angle was also obtained where a second observer would hold the goniolens along with a direct ophthalmoscope (Heine, Optotechnik, Germany) which would provide a focused beam of light onto the superior gonio-mirror and the primary observer would advance the ASPI to capture
the angle image. All images were graded from 1 to 5 according to Noise, Sharpness, Contrast, Diagnostic confidence, Artifacts, Blotchy appearance by 3 individual medical officers with at least 3 years of experience as a consultant.

Results

Clear and magnified images utilizing our ASPI gonio-imaging technique were obtained from 120 patients. This technique was also found to be replicable by different observers. Mean score and SD of each image with ASPI gonio was 10.25, 1.08 and for SLIT lamp it was 9.5 and 1.11. There was no statistical difference between image qualities of ASPI Gonio and slitlamp photography. (p Value-3.53).

Discussion

The use of mobile ophthalmic imaging devices has been an asset in revolutionizing ophthalmic care with the incorporation of smartphones having taken a major leap over the last decade. In recent times, smartphones have aided as an adjunct to clinical examination and are often used for imaging the ocular anterior or posterior segment. There is an increased urge to develop compact health monitoring systems especially in small clinical setups or peripheral health centres. In non-ideal clinical setups, smartphones are often used to document external photographs of the eye especially in emergency rooms. It can be used in patients in supine position as opposed to slit-lamps which are static and require the patient to sit in front of the examiner. They also provide a convenient way of delivering information regarding ophthalmic conditions and treatment options to
patients and their families. Assessment of the anterior chamber angle and its imaging and documentation in glaucoma is of cardinal importance. The use of smartphone for imaging the anterior chamber angle has been described previously. Kumar et al described unaided smartphone based gonio-imaging where a 4-mirror goniolens was placed on the patient's cornea and the angle was photographed with the patient being in supine position. They obtained clear images of all quadrants in 65% of patients, however the images were obtained using diffuse illumination, the study field was large with subtle findings being missed. Pujari et al in their report used the wide angle mode of a high resolution smartphone (iPhone 11 Pro Max) clipped with a macro lens to obtain better quality magnified images and videos. They also performed corneal wedge examination and documentation using the slit beam of a slit lamp as well as that of a direct ophthalmoscope. Their technique however required the use of a relatively expensive smartphone. We have utilised an intraocular lens as a magnifying lens attached to a smartphone camera and obtained high resolution, clear and magnified images of the anterior chamber angle thereby expanding the use of ASPI for gonio-imaging. Our technique of gonio-imaging using ASPI could be performed with the patient in supine as well as sitting position. Diffuse light of the smartphone could be used for imaging the angle as well as slit beam of light from a direct ophthalmoscope could be used for imaging the corneal wedge and hence grading of the angle could also be performed. The other advantages of utilizing ASPI include employing any smartphone, using expired, unsterile IOLs including those with broken haptics. Our technique of imaging is quick, inexpensive and can be readily carried out in peripheral
Eye care centres or in camps as a screening tool as well as to assess the anterior chamber angle before dilatation. It is of a huge advantage in primary or secondary eye care centres where expensive slit-lamp based photography is unavailable and is also of valuable use in resident training and education as well as for obtaining a specialist opinion. To conclude, we broaden the use of ASPI as a cost-effective tool for screening, imaging, documentation as well as grading of the anterior chamber angle and thereby adding it in the armamentarium of smartphone gonio-imaging techniques. 7

References


**Figure Legends**

**Figure 1:**

(A) A 20D IOL attached to the smartphone camera (ASPI) used for gonio-imaging (B, C) ASPI assisted gonio-imaging using a 4 mirror goniolens with the patient’s chin resting on the slit lamp; (D, E) ASPI assisted gonio-imaging with the patient in supine and sitting position respectively thereby showing the ease of use by a single observer.

**Figure 2:**

Gonio images obtained using ASPI showing (A) Superior wide open angle;
(B) High magnification gonio-image of the enclosed area shown in the first figure revealing all the angle structures from bottom to top (arrows) CB – ciliary body band, TM – trabecular meshwork, SS – scleral spur; (C) internal ostium and surgical iridectomy in a post trabeculectomy eye; (D) High magnification of the enclosed area in the previous figure revealing all angle structures clearly along with internal ostium (IO) and surgical iridectomy (SI); (E) Accumulation of emulsified silicone oil seen in the superior angle; (F) Open angle visualised using the thin slit light source of a direct ophthalmoscope.

Fig.1

Fig 2
CONJUNCTIVAL INFLAMMATORY MARKERS IN PRIMARY OPEN ANGLE GLAUCOMA & PRIMARY ANGLE CLOSURE GLAUCOMA

Objective:

Compare conjunctival cellular & inflammatory profile (quantitative & qualitative) in POAG & PACG patients undergoing trabeculectomy

Material & Methods:

30 eyes scheduled for trabeculectomy (15 POAG & 15 PACG), underwent Conjunctival biopsy. Cellular profiling of conjunctiva done with Haematoxylin Eosin, PAS & Masson’s trichrome stain, along with CD3, CD20 & CD68 markers.

Results:

Cellular profile in PACG with median CD68+ at 6.7 was significantly less than controls 19.2(p=0.002) & non significantly less than POAG with median 9.3
Cellular profile in PACG with median CD20+ at 6 was significantly more than controls at 0 (p=0.019) & non significantly more than POAG with median at 3.6

Cellular profile in PACG with median CD3+ at 20 was significantly more than controls at 5.7 (p=0.029) & POAG with median at 19.1 was significantly more than control 5.7(0.021). POAG vs PACG was not significant.

Cellular profile in PACG with median goblet cells at 3 was non significantly less than POAG at 10 & equal to control at 3.

All inflammatory cells were superficial with patchy distribution in 63 %.

Conjunctival fibrosis present in 1/4th (26%) in both POAG & PACG, was mild in 13 % to intense in 40%. Fibrosis in 40 % controls.

**Conclusion:**

Conjunctive of PACG & POAG patients had comparable conjunctival cellular profile although with respect to controls CD3+, CD20+ were more & CD68+ were less.

**INTRODUCTION**

Glaucoma is the leading cause of irreversible blindness in the world with an estimated 34 million people worldwide being affected by 2040 (1).Glaucoma can be classified into primary and secondary type which decides treatment protocol. Primary angle closure glaucoma (PACG) is a major form of glaucoma in East Asia (2) while primary open angle glaucoma (POAG) predominates in Caucasians and African (3,4). Recent studies in India report a high prevalence of PACG at 4.3% (5,6). This subtype blinds more people
than POAG, despite the latter entity being more prevalent worldwide(7).

Trabeculectomy surgery still remains the most commonly performed surgery for glaucoma recalcitrant to medical therapy. The surgery creates a new path for aqueous outflow which bypasses the diseased trabecular meshwork to form a subconjunctival bleb. Bleb functionality and longevity is determined by extent of subconjunctival fibrosis, the latter being the commonest cause of bleb failure. Conjunctiva being the reservoir of fibroblast recruitment at the time of filtration surgery, its preoperative health is likely to play a crucial role in tissue behaviour in response to trauma of surgery.

Primary angle closure glaucoma (PACG) eyes have been documented to present with higher Intraocular pressure (IOP). Recurrent bouts of high IOP in these eyes result in ischemia and reperfusion injury, manifesting with iris atrophy and subclinical inflammation in conjunctiva of ACG eyes. Anatomical aspects of ACG with smaller eyeballs, smaller palpebral fissure and shallow fornices, thicker iris and thicker lens also make trabeculectomy challenging. Concomitant tear film dysfunction subsequent to long term use of anti-glaucoma medications (AGM) resulting in deranged conjunctival milieu and thus reduces chance of bleb survival. Due to the above reasons, filtering surgery in PACG behaves differently from POAG eyes.

Keeping the large volume of PACG patients in India, it's tendency to cause more blindness, and surgical differences in mind, we studied trabeculectomy outcomes in angle closure glaucoma versus open angle glaucoma with respect to bleb morphology and function. Conjunctival cellular profile was
studied for cell markers of inflammation and linkage to bleb survival. There is paucity of data in Indian population comparing trabeculectomy outcomes in Primary Angle Closure Glaucoma and Primary Open Angle Glaucoma. Also, paucity of data on relationship of conjunctiva cellular profile with respect to bleb functionality and morphology in Primary Angle Closure Glaucoma eyes has been noted. Current study aims to compare surgical outcome of trabeculectomy in Primary Angle Closure Glaucoma and Primary Open Angle Glaucoma eyes and correlate conjunctival cellular profile with bleb function and morphology.

MATERIAL AND METHODS

Current study was a hospital based Prospective Comparative study conducted in Department of Ophthalmology, Guru Nanak Eye Centre, New Delhi. In this study patients with uncontrolled primary glaucoma requiring trabeculectomy aged >18 years & patient willing to follow up for minimum 4 months were included. All patients with prior incisional surgery involving conjunctiva, dry eyes, using long-term topical steroids, chronic ocular pathology like keratitis, uveitis, episcleritis and scleritis were excluded. Primary outcome evaluated was Bleb functionality and morphology & conjunctival cell profile. Secondary outcome evaluated was conjunctival inflammation correlation with bleb function and morphology.

Suitable patients meeting the inclusion criteria were enrolled in the study and evaluated on the below mentioned parameters prior to the surgery. Patients were divided into two groups POAG & PACG undergoing trabeculectomy (15 patients each). Trabeculectomy with releasable sutures
with use of mitomycin C (0.02% for 2 min) restricted to patients younger than 50 years, was performed by the same surgeon. A conjunctival frill incision followed by a triangular superficial flap of 4 X 4mm followed by 2X1 mm sclerostomy by Kelly Descemet punch and large peripheral iridectomy was done. The scleral flap was closed by one fixed and 2 releasable sutures. Conjunctival closure by 8-0 nylon was followed by on table titration of bleb. The conjunctival tissue biopsy was taken from inferior conjunctiva of size 2X3 mm at the time of trabeculectomy. The tissue was immediately fixed in 10% buffered formalin and processed as per protocol to have formalin fixed paraffin embedded (FFPE) tissue. Thin sections of 3 microns were cut. Care was taken to orient sections to obtain epithelium and stroma. Cut sections were stained for haematoxylin and eosin and PAS with Diastase with Alcian blue. Immunohistochemistry was performed as per protocol of various primary antibodies (T lymphocytes -CD3, B lymphocytes- CD20 & Macrophages-CD68). With light microscopy cells were counted at 40 magnifications using a micrometer eyepiece, each field representing a surface of 0.1 mm². Inflammatory cell counts were performed in the conjunctival stroma in four different fields and averaged to obtain the representative mean cell count of the labelled immunocompetent cells. Inflammatory cells in blood vessels were not counted. All specimens were observed in a masked manner by one examiner. The average values (mean, median & standard deviation) of cell counts in all groups were calculated. Parameters evaluated were -Intraocular pressure (IOP): measured by Goldman Applanation tonometry (GAT), Conjunctival biopsy: Cellular profile: macrophages (CD68), lymphocytes (CD3, CD20) fibroblast
(Haematoxylin & Eosin), goblet cell (PAS with diastase with Alcian blue), Best corrected visual acuity (BCVA), Slit lamp examination: AC reaction: Standard Uveitis Nomenclature (SUN Classification), Cataract state (LOCS), Bleb morphology assessment: IBAGS, Anterior segment optical coherence tomography (ASOCT): Bleb characteristics evaluated were-Bleb wall thickness at - i) 12 O’ clock position ii) At area of greatest height, Bleb reflectivity was evaluated throughout bleb area, Ocular surface Disruption: by Tear Break Up Time (BUT) and keratometry, Complications during or after surgery including the requirement for Bleb needling, Visual fields examination by Humphrey field analyser 24-2/10-2 as required, Number of anti-glaucoma medications used. Patients were then subsequently evaluated on post- operatively on Day 7, 1 month, and 4 months.

Complete success of trabeculectomy was defined as IOP ≤21 mmHg without any additional medication, whereas qualified success was defined as IOP ≤21 mmHg with or without medication. Failure was defined as uncontrolled IOP >21 mmHg despite medical treatment, or when an additional intervention (such as repeat trabeculectomy, or diode laser cyclodestruction, etc.) was required.

**STATISTICAL ANALYSIS**

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test were used.

Statistical tests were applied as follows- Quantitative variables were
compared using Unpaired t-test/Mann-Whitney Test (for non-normal distribution of data sets) between the two groups. Qualitative variables were compared using Chi-Square test/Fisher’s exact test. A p value of <0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis done using Statistical Package for Social Sciences (SPSS) version 25.0.
RESULTS AND OBSERVATIONS

Comparison of trend of IOP in both groups is shown in table:

Table: Comparison of IOP between pre-operative and post-operative cases in POAG & PACG. n = 15 each group

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pre-operative</th>
<th>Post-operative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre vs Post 1 week:</td>
<td>Pre vs Post 4 weeks:</td>
</tr>
<tr>
<td>Mean ± SD (POAG)</td>
<td>40.27 ± 12.44</td>
<td>17.2 ± 9.06</td>
</tr>
<tr>
<td>Mean ± SD (PACG)</td>
<td>35.2 ± 10.5</td>
<td>15.47 ± 5.58</td>
</tr>
</tbody>
</table>

Fisher’s exact test, ¶ Paired t test
No statistically significant difference in POAG vs PACG at any time interval. 

Success rate of trabeulectomy in current study is depicted in table:

Table: Comparison of success rate between POAG & PACG at 4 months follow up

<table>
<thead>
<tr>
<th>Success &amp; failure rate</th>
<th>POAG (n=15)</th>
<th>PACG (n=15)</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-operative 4 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete success</td>
<td>11 (73.3%)</td>
<td>8 (53.3%)</td>
<td>19 (63.3%)</td>
<td>0.386†</td>
</tr>
<tr>
<td>Qualified success</td>
<td>4 (26.7%)</td>
<td>7 (46.7%)</td>
<td>11 (36.7%)</td>
<td></td>
</tr>
</tbody>
</table>

† Fisher's exact test

In current study 22 (73.3%) patients were using 3 antiglaucoma medications.

12 (80%) POAG patients compared to 10 (66.67%) PACG patients used 3 antiglaucoma medication before trabeculectomy. There was no statistically significant difference between 2 groups (p=0.56). AGM were taken for a mean duration of 8±1.25 Months in POAG vs 6.75±2 months in PACG. It was not statistically significant.

POAG group blebs had tendency to achieve low to medium height at 4 months. Around 60% (9) with medium height, 33.35% (5) low height, 6.7% (1) each having flat and high bleb at 4 months. Mild-moderate vascularity was seen, with 60% (9) moderate vascularity, 33.4% (5) mild vascularity & 6.7% (1) avascular cystic bleb at 4 months. Most blebs at 86.7 % (13) had
extent of more than or equal to 4 clock hours whereas 13.3\% (2) had extent of 3 clock hours.

No patient had any bleb leak till last follow up (Seidel’s negative).

PACG group blebs had tendency towards achieving low to medium height at 4 months with 80\% (12) medium height, 13.3\% (2) low height & 6.7\% (1) high bleb. Mild-moderate vascularity was common, with 66.7\% (10) moderate vascularity and 33.34\% (5) mild vascularity. Bleb extent of more than or equal to 4 clock hours was seen in 73.34\% (11) and 26.7\% (4) extent of 3 clock hours. No patient had any bleb leak till last follow up (Seidel’s negative). No statistically significant difference was seen in bleb morphology between the 2 groups.

In POAG group, 66.7\% (10) patients had high reflectivity & 33.3\% (5) low reflectivity.

Morphology pattern: Filtering bleb with microcysts 86.7\% (13), 6.67\% (1) cystic & 6.67\% (1) flat

Mean height: 567.5 ± 28 \text{µ} \text{microns (4weeks)} & it was 540.2 ± 242.1 \text{µ} \text{at 4 months.}

Bleb wall thickness at 12 o clock: 326.13 ± 119.6 \text{µ (4weeks)} & 308.73 ± 111.7 \text{µ (4 months)}.

Bleb wall thickness (at maximum height): 321.9 ± 113.2 \text{µ(4weeks)} & 304.1 ± 97.6 \text{µ(4 months)}.

In PACG group: 66.67\% (10) patients had high reflectivity & 33.33\% (5) had low reflectivity. Morphology pattern: 93.33\% (14) had filtering bleb with
microcysts, 6.67% (1) had cystic bleb. Mean height: at 4 weeks was 538.73 ± 136.69 µ & at 4 months it was 516.53 ± 118.55 microns. Bleb wall thickness at 12 o clock: at 4 weeks was 283.53 ± 99.47 microns & at 4 months it was 284.47 ± 90.7 microns. Bleb wall thickness at maximum height: at 4 weeks was 285.93 ± 90.1 microns & at 4 months it was 281.27 ± 89.28 microns. There was no statistically significant difference between 2 groups in any of ASOCT parameters.

Comparison of astigmatism in both groups is shown in table

**Table: Comparison of astigmatism between pre-operative and post-operative in POAG & PACG (n=15 each)**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pre-operatively</th>
<th>Post-operatively</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 week</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.62 ± 0.36</td>
<td>2.95 ± 1.46</td>
</tr>
<tr>
<td>(POAG)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>Pre vs Post 1 week: 0.0001</td>
<td>Pre vs Post 4 weeks: &lt;.0001</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.68 ± 0.39</td>
<td>3.72 ± 3.12</td>
</tr>
<tr>
<td>(PACG)</td>
<td>p value</td>
<td>Pre vs Post 1 week: 0.003*</td>
</tr>
<tr>
<td>--------</td>
<td>---------</td>
<td>----------------------------</td>
</tr>
</tbody>
</table>

*Fisher’s exact test, * Paired t test

There was no statistically significant difference between 2 group (p=0.15).
TBUT assessment is shown in Table:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pre-operative</th>
<th>Post-operatively</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 week</td>
</tr>
<tr>
<td>Mean ± SD (POAG)(n=15)</td>
<td>10.4 ± 2.85</td>
<td>7.6 ± 1.8</td>
</tr>
<tr>
<td>p value</td>
<td>Pre vs Post 1 week:0.001†</td>
<td>Pre vs Post 4 weeks:&lt;.0001¶</td>
</tr>
<tr>
<td>Mean ± SD (PACG) (n=15)</td>
<td>9.4 ± 2.03</td>
<td>6.6 ± 1.35</td>
</tr>
<tr>
<td>p value</td>
<td>Pre vs Post 1 week:0.0009¶</td>
<td>Pre vs Post 4 weeks:0.0009¶</td>
</tr>
</tbody>
</table>

Table: Comparison of TBUT between pre-operative and post-operative in POAG.

† Fisher's exact test, ¶ Paired t test

Comparison between POAG & PACG was not statistically significant.

The mean deviation value in visual fields in preoperative period ranged from 2.56-33.58 decibel. In preoperative period, in POAG group MD value was -19.78 ± 12.08 decibel. At post op 4 months the value deteriorated to 20.56 ± 12.28 decibels, that is a change of 0.77 ± 0.63 decibals. This change was
statistically significant (p=0.002). In PACG group, mean MD value was 24.03 ± 7.29 decibels in preoperative period which deteriorated to 25.25 ± 8.08 decibels at 4 months postoperatively, that is a change of 1.87 ± 3.22 decibels. This change however not statistically significant (p=0.1). Also, there was no statistically significant difference between the 2 groups in preoperative (p=0.327) & postoperative period (p=0.3).

Intraoperatively we observed that 26.67% (4) patients in PACG group and 20% (3) patients in POAG group had anterior chamber bleeding. The difference was not statistically significant. At 1 week post-surgery, 16.67% (5) patients had hyphema, 20% (3) in POAG group & 13.33% (2) in PACG group. 16.67% (5) patients had shallow AC, 20% (3) in POAG group & 13.33% (2) in PACG group. 13.33% (4) patients had low IOP, 20% (3) in POAG group & 6.67% (1) in PACG group. In PACG all cases with intraoperative bleeding achieved complete success. In POAG 60% cases achieved complete success 40 % qualified success at 4 months follow up. 6.67% (1) had cystic bleb in PACG group. 6.67% (1) had overhanging bleb in PACG group while 20% (3) patients of POAG group had congestion at 4 weeks post-surgery. At 4 months post-surgery, 26.67% (8) patients had cataract progression, 20% patients (3) of POAG group & 33.33% (5) in PACG group. 20% (6) patients had high IOP, in 26.67% (4) of POAG group & 13.33% (2) in PACG group. 6.67% (1) had cystic bleb in PACG group & 6.67% (1) of POAG had bleb scarring. While 6.67% (1) of POAG had subepithelial keratitis. However, there was no statistically significant difference among 2 groups with respect to complications.

In our study conjunctival biopsy sample was evaluated. Three patterns were
defined -normal, inflammatory & fibroblastic pattern.

Histopathological pattern evaluation is shown in table:

Table: Histopathology pattern comparison in conjunctival biopsy between POAG, PACG and control.

<table>
<thead>
<tr>
<th>Pattern</th>
<th>POAG (n=15)</th>
<th>PACG (n=15)</th>
<th>Control (n=5)</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibroblastic</td>
<td>9 (60%)</td>
<td>9 (60%)</td>
<td>5 (100%)</td>
<td>23 (65.7%)</td>
<td>0.379†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>POAG vs PACG: 1†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>POAG vs Control: 0.44 2‡</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>5 (33.3%)</td>
<td>6 (40%)</td>
<td>0 (0%)</td>
<td>11 (31.4%)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1 (6.7%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (2.9%)</td>
<td></td>
</tr>
</tbody>
</table>

† Fisher’s exact test

Table: Comparison inflammatory markers between POAG, PACG & control.

<table>
<thead>
<tr>
<th>Conjunctiva biopsy</th>
<th>POAG (n=15)</th>
<th>PACG (n=15)</th>
<th>Control (n=5)</th>
<th>P value</th>
</tr>
</thead>
</table>

193
<table>
<thead>
<tr>
<th>CD3+</th>
<th>POAG vs PACG: 0.859</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (25th-75th percentile)</td>
<td>19.1 (13.3-29.9)</td>
</tr>
<tr>
<td>CD20+</td>
<td>POAG vs PACG: 0.308</td>
</tr>
<tr>
<td>Median (25th-75th percentile)</td>
<td>3.6 (2.1-7.6)</td>
</tr>
<tr>
<td>CD68+</td>
<td>POAG vs PACG: 0.075</td>
</tr>
<tr>
<td>Median (25th-75th percentile)</td>
<td>9.3 (6.4-14.2)</td>
</tr>
</tbody>
</table>

**Krystal Wallis test followed by post hoc Dunn test**

**Table: Comparison of goblet cells between POAG, PACG & control.**

<table>
<thead>
<tr>
<th>Conjunctiva biopsy</th>
<th>POAG (n=15)</th>
<th>PACG (n=15)</th>
<th>Control (n=5)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (25th-75th)</td>
<td>10 (2-23)</td>
<td>3 (0-8.5)</td>
<td>3 (1-6)</td>
<td>POAG vs</td>
</tr>
</tbody>
</table>
Connective tissue studied in conjunctival biopsy specimen was divided into 3 main types - excessively loose, mixed loose & dense and predominantly loose with focal thickening.

The comparison of POAG & PACG group respectively with control group as
well as with each other was not statistically significant.

**Table: Comparison of fibrosis between POAG, PACG & control.**

<table>
<thead>
<tr>
<th>Conjunctiva biopsy</th>
<th>POAG(n=15)</th>
<th>PACG(n=15)</th>
<th>Control(n=5)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No fibrosis</td>
<td>11 (73.3%)</td>
<td>12 (80%)</td>
<td>3 (60%)</td>
<td>POAG vs PACG:1†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>POAG vs Control:0.613†</td>
</tr>
<tr>
<td>Fibrosis present</td>
<td>4 (26.7%)</td>
<td>3 (20%)</td>
<td>2 (40%)</td>
<td>PACG vs Control:0.56†</td>
</tr>
</tbody>
</table>

Fisher’s exact test, ‡ Chi square test, § ANOVA

**Table: Comparison of inflammation between POAG, PACG and control.**

<table>
<thead>
<tr>
<th>Inflammation</th>
<th>POAG</th>
<th>PACG</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No inflammation</td>
<td>7 (46.7%)</td>
<td>7 (46.7%)</td>
<td>0(0%)</td>
<td>POAG vs PACG:1†</td>
</tr>
<tr>
<td>Mild inflammation</td>
<td>2 (13.3%)</td>
<td>2 (13.3%)</td>
<td>0(0%)</td>
<td></td>
</tr>
<tr>
<td>Moderate inflammation</td>
<td>0(0%)</td>
<td>0(0%)</td>
<td>0(0%)</td>
<td></td>
</tr>
<tr>
<td>Intense inflammation</td>
<td>6 (40%)</td>
<td>6 (40%)</td>
<td>0(0%)</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td>Superficial</td>
<td>Deep</td>
<td>No p value</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>-------------</td>
<td>------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 (100%)</td>
<td>0(0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uniform/patchy</td>
<td>Patchy</td>
<td>Uniform</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (62.5%)</td>
<td>3 (37.5%)</td>
<td>POAG vs PACG:1†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (62.5%)</td>
<td>3 (37.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0(0%)</td>
<td>0(0%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† Fisher's exact test

Goblet cells-stained magenta pink (arrow) with Periodic Acid Schiff-Diastase stain (magnification 40X)
Mixed loose & dense connective tissue (arrow) stained with Massone Trichrome stain

Dense inflammatory infiltrate (arrow) on Hematoxylin-Eosin stain.
(Magnification 40X)
CD3+ cells stained brown (magnification 40X) on immunohistochemistry.

CD20+ cells stained brown (magnification 40X) on immunohistochemistry.
CD68+ cells stained brown (magnification 40X) on immunohistochemistry.

**DISCUSSION**

The principal aim of this study was to compare surgical outcomes of trabeculectomy in POAG versus PACG and correlation with the conjunctival inflammatory markers. Trabeculectomy remains the gold-standard surgical method for reduction of intraocular pressure (IOP) in the management of glaucoma(8).

Mean age of study was 42.37 ± 13.58 years (in POAG) and mean age 38.8 ± 14.79 years (in PACG). All patients in POAG group were males, whereas PACG group comprised of 60% males & 40% female. Positive family history of glaucoma was present in 27% of POAG cases (4/15) and none in PACG cases. Mean value of CCT was 541.5 ± 32μ (in POAG) versus 538.2 ± 29.5 μ (in PACG). Difference Not Significant statistically.

Visual acuity was retained for most (87%) patients with no intergroup difference.

Post-surgery the reduction of IOP was similar for POAG at 17.9 ± 6.2 mmHg (4 weeks) and 18.3 ± 5.4 mmHg (4 months) and PACG group at 16.7 ± 2.5 (4 weeks) and 19.07 ± 5.01 mmHg (4 months). Maheshwari D et al, while studying similar group over a 3-year period reported significant improvement in BCVA in ACG compared to OAG group, attributed to a higher number of cataract surgeries performed in the ACG group(9). Complete success was attained in 63.3% patients and qualified success in 36.7%. More POAG trabeculectomy were completely successful at 73.3% compared to 53.3% PACG cases, however the inter group difference was Not Significant.
Maheshwari D et al have also reported higher success rates for trabeculectomy in OAG at 68% compared to 55 % in ACG, over a longer follow up of 3 years\textsuperscript{8}. They attributed this to more postoperative complications in PACG particularly cataract extraction resulting in poor IOP control\textsuperscript{9}. Sihota R on the other hand with a longer follow-up of 10-year, reported similar success rates of trabeculectomy in PACG and POAG\textsuperscript{10}. A life-table analysis in a Japanese population also showed comparable 5-year control rates between POAG and PACG eyes, with no racial differences in Asians and Caucasians\textsuperscript{10}. The current study required bleb needling to revive bleb in 2 cases of POAG group and one case of PACG.

In current study, both group blebs had tendency to achieve low to medium height, moderate-mild vascularity, extent of more than or equal to 4 clock hours at 4 months follow up. NS. Bleb vascularity, bleb extent had positive correlation with IOP and bleb height negative correlation with IOP in POAG trabeculectomy NS. For PACG group bleb height, vascularity & extent all had negative correlation with IOP, correlation not attaining statistical significance. Overall IOP was significantly better controlled in microcystic blebs & low reflectivity blebs at 4 months follow up although intergroup no significant difference could be elicited. Cvenkel B et al and Ciancaglini M et al correlated successful trabeculectomy with greater area and decreased bleb vascularity, with diffuse and cystic blebs being associated with low IOP\textsuperscript{11,12}. No study has prospectively compared bleb morphology in ACG versus OAG, previously. Current study shows that overall IOP was significantly better controlled in microcystic blebs & low reflectivity blebs at 4 months follow up although intergroup no significant difference was
elicited. Also, current study found not statistically significant better IOP control with low bleb height & low bleb wall thickness in both groups at 4 months follow up. Bleb functionality studies by Ciancaglini M et al, Kawana et al & Pfenninger L et al have identified large internal fluid filled cavity, extensive hypo reflective area, multiform blebs and thicker bleb walls with more microcysts with successful blebs(12–14). Detailed studies by Singh M et al have linked bleb height, bleb wall thickness, cystic spaces within bleb wall to successful blebs(15). Other authors have confirmed bleb wall thickness to be negatively correlated with IOP(15,16). Reflectivity of the bleb wall, measured by AS-OCT and width of filtration opening at an early stage have emerged as early post-trabeculectomy predictors of bleb outcome(17,18). Low reflectivity of bleb wall, presence of posterior episcleral fluid have been associated with lower IOP(14,16).

Astigmatism increased at 1 week postoperative period in both groups and remained at 4 weeks despite removal of releasable sutures. Tear film disruption was noted. There were improved TBUT readings over time, but residual TBUT reduction remained till 4 months. Intergroup difference at all times was NS in both groups. Number of AGM had negative correlation with preoperative TBUT in both groups. NS. Sherwood M reported higher grades of conjunctival metaplasia, abnormal presence of inflammatory cells and expression of immune markers by epithelial cells in patients on long term therapy with various anti-glaucoma drugs(19).

Subconjunctival fibrosis due to faster and exuberant wound healing is the most common cause of failure of trabeculectomy(8,20). Bleb failure often
occurs during early postoperative months due to hyper-cellular response characterized by inflammation and fibroblast proliferation, migration, and extracellular matrix deposition (8,21). Broadway D et al in their exhaustive study on reviewing risk factors for filtration failure and possible underlying perioperative conjunctival cellular mechanisms, proposed that preoperative state of the conjunctiva, which acts as a reservoir for fibroblast recruitment played a crucial role in tissue response to surgical trauma (8). The relationship between conjunctival cellular profile and risk factors for trabeculectomy failure identified before surgery are critical in development of targeted, patient specific, wound healing modulators (8).

Conjunctival biopsy specimens from long-term treated patients with glaucoma confirm thicker conjunctival epithelium, fibroblastic infiltration, and indications of chronic inflammation (22,23). Baudouin C et al. used impression cytology & cytochemistry to demonstrate increased expression of inflammatory membrane markers (HLA-DR class II antigens, low-affinity receptor of IgE (CD23) in conjunctival cells in patients on long term AGM therapy (22).

Fibrous pattern was seen in 26% of glaucoma cases (27% patients of POAG, 20% patients in PACG). Inter group comparison NS.

Cells positive to CD3+ (T Lymphocytes) were at 5.7 (control), 19.1 (POAG) & 20 (PACG). Comparison of POAG with control (p=0.021) and PACG with control (p=0.029) was statistically significant. Comparison of POAG & PACG was NS. Cells positive to CD20+ (B Lymphocytes) were at 0 (control), 3.6 (POAG) & 6 (PACG). Comparison of PACG with controls was statistically
significant (p=0.019), while POAG vs controls was not statistically significant. POAG vs PACG did not achieve statistical significance. Cells positive to CD68+ (Macrophages) were 19.2 (control), 9.3 (POAG) & 6.7 (PACG). Comparison of POAG group with control was NS, however that of PACG with control did show statistically significant difference (p=0.002). POAG vs PACG was not statistically significant. Number of goblet cells were 3 (control), 10 (POAG) & 3 (PACG). Comparison of both POAG & PACG with controls was NS. POAG vs PACG was NS.

No significant correlation between cell profile & ASOCT Bleb morphology parameters could be inferred from current study.

Almost 73 % (22/30) patients were on 3 antiglaucoma medications (80% POAG patients and 67% PACG patients). Four AGM were used by 20 % (13% POAG and 26 % PACG). Inter group difference was not statistically significant. No statistical correlation could be drawn between inflammation grade and no of AGM used.

Around 47% of glaucoma patients and 100% of control group were found to have no inflammation. Mild inflammation was seen in 13.3% of patients (POAG & PACG group) and intense in 40% (POAG & PACG group). Inflammation was superficial in all with patchy pattern in 63% & uniform in 38% cases for both POAG & PACG groups. Intergroup comparison of POAG & PACG group NS. A study by Broadway D et al, found that patients briefly treated (AGM duration less than 2 months) with medications fared as well after trabeculectomy as did the group treated with beta-blockers, with success rates of 90% at minimum follow up of 6 months’ time(8). Addition
of miotics however reduced surgical success rate to 72%, with lowest success at 45% for group treated with beta-blockers, miotics, and sympathomimetics combination (8). It is evident from the above that long-term topical combination therapy posed significant risk factor for failure of trabeculectomy.

No definitive statistically significant correlation between no. of AGM & cellular profile could be inferred from current study.

Broadway D et al analysed preoperative subclinical conjunctival inflammation by conjunctival biopsy induced by previous topical medication, and found conjunctiva receiving combination therapy (beta blocker, miotic & sympathomimetic) having significant decrease in goblet cell; increased macrophages, lymphocytes in epithelium with increased fibroblasts, macrophages, mast cells, and lymphocytes in substantia propria (8). Duration of therapy, irrespective of type, for 3 years or more was noted to result in greater subclinical inflammation (8).

Sherwood M et al in their study demonstrated high concentrations of macrophages, lymphocytes (both intraepithelial and subepithelial), mast cells, fibroblasts, as well as a decrease in goblet cell density in patients receiving anti-glaucoma drugs for 7.7 years, compared to patients with virgin conjunctiva (19). Baudouin C also found significant cell infiltrations in conjunctiva of patients receiving one beta-blocker for several years but were unable to show a difference between treatments duration of greater than or less than 3 years (22).

The fibroblast number had positive correlation with IOP in both POAG and
PACG groups, however not statistically significant.

At 4 weeks - For POAG group 31% and 38% patients with pre-operative sub conjunctival fibrosis went on to form filtering bleb morphology and high reflectivity on ASOCT respectively. For PACG group 14.3 and 33.3 % with preoperative conjunctival fibrosis went on to form a filtering bleb morphology and high reflectivity on ASOCT respectively.

At 4 months (last follow up) - For both PACG & POAG group: All patients with no pre op fibrosis went on to develop blebs with low reflectivity on ASOCT. Almost 40% (POAG) & 30% (PACG) patients with pre op conjunctival fibrosis developed blebs with high reflectivity. 31% (POAG) and 14% (PACG) of filtering bleb on ASOCT had fibrosis. Inter group difference did not attain statistical significance at any point.

The number of cells CD3, CD68 had negative correlation with preoperative IOP in both groups. These associations were not statistically significant. The number of goblet cells had non-significant positive correlation with preoperative IOP in both groups.

Mean deviation value in visual fields at preoperative level ranged from 2.56-33.58, with value of -19.78 ± 12.08 decibel in POAG group. At 4 months post-operative value the MD was 20.56 ± 12.28 decibels, a 0.77 ± 0.63 decibel, statistically significant change (p=0.002). In PACG group, mean MD value was 24.03 ± 7.29 decibels in preoperative period which reduced to 25.25 ± 8.08 decibels by 4 months, change of 1.87 ± 3.22 decibels, difference not being statistically significant.

Postoperative complications are found be no different in trabeculectomy
done for PACG and POAG.

Current study was not without limitations. Sample size was small, with 15 patients in each group with short follow up of 4 months. This curtailment was due to COVID 19 pandemic and patient lost to follow up. Further studies for large group over a longer follow up are needed to substantiate the findings of current study.

Trabeculectomy surgery helps in IOP control with better results in POAG compared to PACG. Complication profile is similar in both cases. Significant association of preoperative inflammation with IOP control could not be proved with this study. CD3+, CD20+ cells were found to be more in both group with respect to controls and CD68 cells were found to be less compared to controls although intergroup POAG vs PACG difference was NS. Further studies with a large sample size and longer follow up is needed to substantiate the findings of this study. Further studies comparing bleb morphology in POAG and PACG cases are needed. Further studies correlating bleb morphology and cellular profile are needed.

REFERENCES


PRIMARY IMPLANTATION OF GLAUCOMA DRAINAGE DEVICE IN SECONDARY GLAUCOMA: COMPARISON OF AADI VS AGV

Abstract

Purpose:

To investigate the comparative efficacy and safety of Aurolab Aqueous Drainage Implant (AADI) and the Ahmed Glaucoma Valve (AGV) when implanted in filtration-surgery-naïve secondary glaucoma eyes.

Methods:

Retrospective review of patients with secondary glaucoma who underwent primary tube procedure, either AADI or AGV. Primary outcome measure was IOP and secondary were BCVA, number of antiglaucoma medications (AGMs), complications.

Results:

Fifty-nine 59 eyes in AADI with follow-up of 20.3±12.9 months and 67 eyes
in AGV with a follow-up of 19.9±18.2 months, were included. Preoperative IOP, AGM, and BCVA did not differ but at last visit, IOP and AGM was significantly lower and complete success significantly higher in the AADI group (all p<.001). Serious complication rates were comparable.

**Conclusions:**

Both procedures were effective in reduction of IOP and need for AGM, but this was significantly so in the AADI group along with higher rate of complete success and therefore this affordable GDD could have a tremendous impact in our country.

**Key words:**

Glaucoma Drainage Device, GDD, Valved GDD, non-valved GDD, tubes, hypertensive phase

**Introduction**

Secondary glaucomas form a significant proportion of all glaucomas and the majority tend to be very refractory to treatment. Such eyes generally tend to have more inflammation (uveitic glaucoma, neovascular glaucoma, silicone oil induced glaucoma etc.) or tend to have membranes growing over the angle to shut it down (neovascular glaucoma, Irido-corneal endothelial syndromes etc.) or tend to have scarred conjunctiva due to previous surgeries (post vitreo-retinal surgeries, post keratoprosthesis etc.) or may have a combination of one or more of these factors. Not only are they poor responders to medical management but quite often fail after trabeculectomy (trab) as well, despite use of adjuvants. Thus, it is not unusual for these eyes
to undergo multiple trabs before a glaucoma drainage device (GDD) is considered or the patient referred on as the technical skill may not be available locally.

Several authors have reported that when such eyes of refractory glaucomas with failed trab/s undergo a GDD, then it too tends to fail. [1-4] Therefore a therapeutic approach that may result in better outcomes in eyes that have refractory secondary glaucoma is to implant GDDs primarily.

The incidence of secondary glaucomas in India has been reported to be at a variable rate – 6% [5] to 21.8%. [6] Although the rate may be unequable, most authors agree that such glaucomas tend to be very refractory to treatment and a sizeable number of such eyes end up with GDD surgery.

The two types of GDD surgery available in India are the Ahmed Glaucoma Valve (AGV, New World Medical Inc., Rancho Cucamonga, California, USA) and the Aurolab Aqueous Drainage Implant (AADI, Aurolabs, India). The AGV is a valved device with a flow restrictor which theoretically remains closed at low intraocular pressure (IOP) and is thus considered to be protective for hypotony. The AADI is an indigenously manufactured, inexpensive, non-valved device, the design inspiration of which is the Baerveldt Glaucoma Device (BGD, Advanced Medical Optics, Santa Ana, California, USA) – 350 mm² model.

Although there are a few studies that have compared AGV and AADI in refractory glaucomas in adults, [7-9] none of these have reported the outcomes of primary implantation of GDD in secondary glaucomas. The objective of this study was to investigate the comparative efficacy and safety
of AADI and AGV when implanted in filtration-surgery-naïve secondary glaucoma eyes.

METHODS

Study design: This was a retrospective, comparative, interventional study wherein a review of charts of consecutive adult patients who underwent GDD surgery and were followed-up between January 2017 to June 2021 by a single fellowship-trained surgeon and who had at least 3 months of documented post-op follow-up, was undertaken. Ethical clearance was obtained from an Independent Ethics Committee; the study adhered to the principles as laid down by the Declaration of Helsinki. Informed written consent for surgery was obtained from all the eligible participants.

Inclusion criteria:

Consecutive AGV/AADI surgery with a minimum of 3 months follow-up.

Exclusion criteria: GDD in those eyes that underwent prior trabeculectomy were excluded and so were those eyes where Goldmann Applanation Tonometry (GAT) was either not possible or compliance was poor (e.g. Kerato-prosthesis, pediatric eyes etc).

Initially a detailed history was obtained from all patients and the eyes underwent a comprehensive examination. This included - best-corrected visual acuity (BCVA) assessment with a Snellen chart, detailed slit-lamp biomicroscopy, intraocular pressure (IOP) assessment with Goldmann applanation tonometry (Zeiss SL 130 slit lamp with Goldmann style applanation tonometer AT 030), gonioscopy with Sussman 4-mirror, dilated
stereo fundoscopy with +66D Volk lens (Volk Instruments, OH, USA). Visual fields, where possible, was documented by the Humphrey field analyser (HFA, Carl Zeiss Meditec, Jena, Germany).

Follow-up visits were scheduled as per clinical indication but for the purpose of the study, data was documented at day 1, week 1, week 6, month 3, month 6 and year 1 and at last follow-up postoperatively.

**Surgical methods:**

Surgical procedure of AADI has been described in detail previously. [8,10] All AADI plates were placed under adjacent recti and none of the plates were trimmed.

For AGV standard implantation between muscles was followed. Under peribulbar block and sterile conditions, a fornix-based conjunctival opening was created, commonly in the supero-temporal (ST) quadrant. The implant was primed and then anchored to the sclera, 10 mm posterior to the the limbus, with a long pass of a preplaced 6-0 vicryl suture (braided coated polyglactin 910 violet: Ethicon, Johnson & Johnson, HP, India). The needle was then threaded through the eyelets on the endplate and it was inserted into the ‘pocket’, positioned between muscles and secured with a knot which was rotated into the fixation eyelet. The tube length was shortened to approximately 3 mm with a bevelled tip opening toward the cornea. A 23-gauge needle was used to create a track 2mm behind the limbus through which the tube was inserted into the anterior chamber just anterior and parallel to the iris for anterior chamber placement and behind the iris for a sulcus placement. The tube was inserted through the needle track and
secured to the sclera with a figure-of-eight 10-0 nylon suture (monofilament polyamide black, Ethilon; Ethicon, Johnson & Johnson, Himachal Pradesh, India).

For both the types of tubes, almost the entire length of the tube was covered with a corneal patch graft, prepared a-priori,[10] or a scleral patch graft. Patch graft was secured over the tube with either fibrin glue or 10-0 nylon suture. The conjunctiva and tenon were then brought forward and secured back into position with 8-0 vicryl, (braided coated polyglactin 910 violet: Ethicon, Johnson & Johnson, HP, India) wing and continuous sutures. After the procedure, a subconjunctival injection of steroid (dexamethasone 4 mg) was given. The eye was patched and removed 24-hrs later.

Post-operatively topical antibiotics moxifloxacin was used four times daily for one week and topical cycloplegic eye drops (Homatropine 2%) was used as per requirement for 1-2 weeks.

Topical steroid drops (difluoro prednisolone butyrate acetate, or DFBA 0.05%) was used 2-hourly for 1 week and thereby tapered slowly over 8 to 12 weeks.

Most significantly, AGM was recommenced in the AGV group in the early post-operative period as soon as IOP>14 mmHg. The AGM commenced were mostly topical aqueous suppressants – beta blockers, carbonic anhydrase inhibitors or alpha-adrenergic agents, either alone or in fixed drug combinations. This was not the therapeutic approach in AADI.

Outcome criteria: Primary outcome measure was IOP and secondary outcome measures were the number of anti-glaucoma medication (AGM),
LogMAR best corrected visual acuity (BCVA) and complications.

Complete success was defined as an IOP ≥ 5 mmHg and ≤ 21 mm Hg. When the above IOP criteria was met with AGM, it was considered as qualified success. Failure was defined as the inability to meet IOP criteria, loss of perception of light, explantation of device or any additional glaucoma surgery to reduce IOP.

Any eye which underwent a re-procedure or which had reduction in visual acuity (VA) of 2 lines or more was considered as a serious complication.

Hypertensive phase was defined by a tense cystic bleb around the plate with much increased height accompanied with IOP ≥21 mmHg with or without AGM, after reduction of IOP to less than 22 mmHg during the early postoperative period and not caused by tube obstruction, from the third week onwards for AGV and post-suture autolysis after the sixth week onwards for AADI.

Statistics:

Descriptive statistics was performed to compare baseline demographic and ocular characteristics of the treatment groups. Descriptive data is presented as Mean±Standard Deviation. Normality was checked via the Shapiro-Wilk test. Accordingly, univariate comparisons were performed using the paired t test or Wilcoxon-Signed rank test within group and Independent t test or Mann-Whitney U test for between-group comparisons. Chi-squared test or Fisher’s exact test was used for categorical variables. Snellen visual acuity was converted to logarithm of minimal angle of resolution (logMAR) for analysis. IOP and AGM data was censored if explanted or second glaucoma
surgery was needed; visual acuity data was not censored. Survival analysis by Kaplan-Meier and risk factors for treatment failure were assessed for statistical significance by Cox proportional hazard. All statistical tests were 2-sided, and statistical significance was defined as p<0.05. Statistical analyses were performed using the statistical software Stata 12.1 (StataCorp, College Station, TX).

Results:

A total of 126 eyes of 119 subjects underwent primary GDD in secondary glaucoma. All the surgeries were performed by a single senior fellowship-trained glaucoma specialist. 59 eyes underwent AADI, and 67 eyes underwent AGV. All the eyes in the AADI group had a follow-up of more than 3 months and were included; 6 of 67 eyes in the AGV had less than 3 months follow-up and were excluded. Mean follow-up was 20.3±12.9 months in the AADI group and 19.8±11.8 months in the AGV group.

Supero-temporal (ST) was the most common quadrant for placement of the GDD in both the groups – 98.4% (n=60) in the AGV group and 91.5% (n=54) in the AADI group. All the rest in both the groups were placed in the infero-temporal (IT) quadrant. 50.8% (n=31) AGV tubes and 40.7% (n=24) AADI tubes were placed in the ciliary sulcus (CS).

11.8% (n=7) eyes underwent simultaneous GDD and cataract surgery in the AADI group and 6.5% (n=4) in the AGV group. An additional 4.9% eyes (n=3) underwent simultaneous flanged technique of sclera fixated intra-ocular lens implant (SF-IOL).

Retinal diseases and surgery related to it formed the largest etiological
category of secondary glaucoma in both the groups. (Table 1)

### Table 1: Etiology of secondary glaucoma between the two groups – Aurolab Aqueous Drainage Implant (AADI) and Ahmed Glaucoma Valve (AGV)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>AADI</th>
<th>AGV n=61</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neovascular glaucoma</td>
<td>12</td>
<td>25</td>
<td>0.055</td>
</tr>
<tr>
<td>Post Retinal surgery</td>
<td>13</td>
<td>19</td>
<td>0.177</td>
</tr>
<tr>
<td>Aphakic/ pseudophakic</td>
<td>6</td>
<td>11</td>
<td>0.423</td>
</tr>
<tr>
<td>Post Corneal Transplant</td>
<td>7</td>
<td>1</td>
<td>0.024</td>
</tr>
<tr>
<td>Uveitis</td>
<td>10</td>
<td>2</td>
<td>0.012</td>
</tr>
<tr>
<td>Others</td>
<td>11</td>
<td>3</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Both groups were well matched in terms of baseline characteristics. (Table2)

### Table 2: Baseline characteristics between the two groups – Aurolab Aqueous Drainage Implant (AADI) and Ahmed Glaucoma Valve (AGV)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AADI n=59</th>
<th>AGV n=61</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>47.2 ± 19.7</td>
<td>45.9 ± 17.0</td>
<td>0.689</td>
</tr>
<tr>
<td>Intraocular pressure in mmHg</td>
<td>35.8 ± 10.6</td>
<td>33.1 ± 11.7</td>
<td>0.139</td>
</tr>
<tr>
<td>Anti-glaucoma (number)</td>
<td>3.8 ± 0.9</td>
<td>4.1 ± 0.7</td>
<td>0.542</td>
</tr>
<tr>
<td>BCVA (LogMAR)</td>
<td>1.1 ± 0.7</td>
<td>1.2 ± 0.7</td>
<td>0.363</td>
</tr>
</tbody>
</table>

Intraocular pressure and anti-glaucoma medications: Table 3 and 4, Figure 1 and 2

### Table 3: Outcomes in Aurolab Aqueous Drainage Implant (AADI) and Ahmed Glaucoma Valve (AGV) groups
Table 4: Baseline and follow-up intraocular pressures (IOP) and anti-glaucoma medications (AGM) for the two groups, Aurolab Aqueous Drainage Implant (AADI) and Ahmed Glaucoma Valve (AGV)

<table>
<thead>
<tr>
<th></th>
<th>AADI IOP</th>
<th>AGV IOP</th>
<th>p value</th>
<th>AADI</th>
<th>AGV</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-op</td>
<td>35.8 ± 10.6</td>
<td>34.8 ± 13.3</td>
<td>0.139</td>
<td>3.8 ± 0.9</td>
<td>4.1 ± 0.7</td>
<td>0.542</td>
</tr>
<tr>
<td>†POD1</td>
<td>22.3 ± 11.7</td>
<td>12.1 ± 5.2</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>‡POW1</td>
<td>20.6 ± 9.6</td>
<td>14.0 ± 7.0</td>
<td>&lt;0.001</td>
<td>1.7 ± 1.2</td>
<td>0.4 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>POW6</td>
<td>9.3 ± 7.6</td>
<td>16.9 ± 6.5</td>
<td>&lt;0.001</td>
<td>0.8 ± 1.4</td>
<td>1.5 ± 1.0</td>
<td>0.002</td>
</tr>
<tr>
<td>§POM3</td>
<td>13.1 ± 4.2</td>
<td>16.0 ± 5.0</td>
<td>0.008</td>
<td>0.6 ± 0.9</td>
<td>1.8 ± 1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>POM6</td>
<td>11.9 ± 3.7</td>
<td>14.8 ± 3.6</td>
<td>&lt;0.001</td>
<td>0.7 ± 1.1</td>
<td>1.7 ± 1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Last</td>
<td>12.9 ± 3.7</td>
<td>15.7 ± 2.7</td>
<td>&lt;0.001</td>
<td>0.6 ± 0.9</td>
<td>1.8 ± 1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>†POD</td>
<td>‡POW</td>
<td>§POM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-op</td>
<td>Post-op</td>
<td>Post-op</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 1. Intraocular pressure (IOP) in Aurolab Aqueous Drainage Implant (AADI) and Ahmed Glaucoma Valve (AGV) groups

![Graph showing the comparison of Intraocular pressure (IOP) between AADI and AGV groups over time. The graph displays data points for pre-op, day 1, week 1, week 6, month 3, month 6, and last f/u, with IOP in mmHg on the y-axis and Time on the x-axis. The graph shows a decline in IOP over time in both groups, with AADI having slightly lower IOP than AGV.]

Figure 2. Number of anti-glaucoma medication/s (AGM) in Aurolab Aqueous Drainage Implant (AADI) and Ahmed Glaucoma Valve (AGV) groups

![Graph showing the number of anti-glaucoma medication/s (AGM) over time in AADI and AGV groups. The graph displays data points for pre-op, day 1, week 1, week 6, month 3, month 6, and last f/u.]
In the AADI group, mean IOP decreased from 35.8 ± 10.6 mmHg at baseline to 12.9 ± 3.7 mmHg at last follow-up (p<0.001); the percentage reduction was 64%. Similarly, in the AGV group, mean IOP decreased from 34.8 ± 13.3 mmHg at baseline to 15.7 ± 2.7 mmHg at last follow-up (p<0.001) and the percentage reduction was 54.8%.

The AGV group had a significantly lower mean IOP than the AADI group at the day 1 and the week 1 follow-up visit (both p <0.001). However, the mean IOP in the AADI group was significantly lower than the AGV group at every post-operative visit thereafter, Table 4.

Similarly, there was a significant reduction in the need for medical therapy in both treatment groups (p<0.001) with a significantly lower need for AGM in the AADI group at every post-operative visit after the week 1 visit. At the final follow-up visit, the percentage reduction in AGM was 84% in the AADI
group and 56% in the AGV group.

Figures 1 and 2 plot the IOP and AGM between groups at various timepoints. Complications: Table 5 enlists all the complications in each group. Notably the early complications and the total number of complications in the AGV group were significantly more than the AADI group, but late as well as serious complications, as defined previously, did not differ between groups.

Table 5:

Table 5: Early and late complications for the two groups, Aurolab Aqueous Drainage Implant (AADI) and Ahmed Glaucoma Valve (AGV)

<table>
<thead>
<tr>
<th>Early complications ≤3</th>
<th>AADI (n)</th>
<th>AGV (n)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyphaema</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Hypotony / Choroidals</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Shallow AC / aqueous</td>
<td>-</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Fibrin / Hypopyon</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>-</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Conj gape / retraction</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Tube block</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Tube / Plate exposure</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Vitreous Haem</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Total early complications</td>
<td>19 (32.2%)</td>
<td>33 (54%)</td>
<td>.015</td>
</tr>
</tbody>
</table>
Table 6: Interventions for all complications and serious complications for the two groups, Aurolab Aqueous Drainage Implant (AADI) and Ahmed Glaucoma Valve (AGV)

<table>
<thead>
<tr>
<th>Interventions for all</th>
<th>AADI (n)</th>
<th>AGV (n)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suturelysis in OR</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Conj suturing / CLAG</td>
<td>2</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Repeat Patch graft</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>CD drainage</td>
<td>2</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Tube trimming /</td>
<td>2</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Vitrectomy (Pars plana, RD surgery)</td>
<td>1 × 1</td>
<td>3 × 1</td>
<td>1 × 1</td>
</tr>
<tr>
<td>Total interventions</td>
<td>9 (15.2%)</td>
<td>15</td>
<td>.201</td>
</tr>
<tr>
<td>Serious Complications (Interventions + VA worse ≥ 2lines or NLP)</td>
<td>13 (22%)</td>
<td>19 (31.1%)</td>
<td>.780</td>
</tr>
</tbody>
</table>

Visual acuity: Almost a similar proportion of eyes in both groups (n=47, 79.7% in the AADI group and n=49, 80.3% in the AGV group; p=0.927) had either no change or an improvement in BCVA. Overall, BCVA improved marginally in both the groups, but this was not statistically significant (p=0.865). One eye in the AGV group lost perception of light but none in the
AADI group did so. Four eyes in the latter had vision worse by more than 2 lines, whereas this occurred in 2 eyes in the former group.

Hypertensive phase: HTP was seen less frequently in the AADI group (n=14, 23.7%) and much more frequently in the AGV group (n=29, 50.8%, p=.006) where it was detected most commonly between 3-6 weeks, despite the use of early aqueous suppressants.

Outcomes:

Complete success was seen in 34 eyes (57.6%) in AADI group and another 20 eyes (33.9%) achieved IOP control with medication (qualified success). Therefore, total success in the AADI group was 54 eyes (91.5%). Complete success was seen in 9 eyes (14.7%) in the AGV group and an additional 40 eyes (65.6%) as qualified success (total success 49 eyes, 80.3%). Thus, even though the overall success was not significantly higher in the AADI group at last follow-up (p=.078), the complete success achieved in the AADI group was statistically significant (p<.001).

A total of 5 eyes failed in the AADI group (8.4%) and 11 eyes (18%) did so in the AGV group (p =0.123). Device explantation was commoner in AADI (n=4) whereas failure on IOP criterion and the need for further glaucoma surgery was higher in the AGV group (n=8). One eye in the AGV group failed on VA criterion, but none did so in the AADI group.

A Kaplan Meier plotting of cumulative probability of complete success was 66%, 60% and 50% in the AADI group at year 1, 2 and 3 respectively whereas it was 22%, 18% and 15% in the AGV group (log rank, p <.001). The total success was 92%, 90% and 82% at year 1, 2 and 3 respectively in the
AADI group and that in the AGV group was 88%, 72% and 62%. Figures 3 and 4 show the Kaplan Meier survival by group for complete and total success.
Cox proportional hazards model was constructed to determine baseline, pre-operative, intra-operative and post-operative characteristics for failure. Hypertensive phase and AGV were found to be significant in multivariate analysis.

Discussion

This retrospective study compared the primary implantation of non-valved
GDD (AADI) and the valved GDD (AGV) in secondary glaucomas which were filtration surgery naïve, and demonstrated that non-valved GDD can achieve significantly lower IOP with much lesser number of AGM when compared to valved AGV. Furthermore, even though the overall success rate did not differ between groups, the complete success rate was higher in the AADI group. Similarly, though the incidence of serious complications did not differ, the early and total complications occurred at a significantly increased rate in the AGV group.

Most studies including the large, randomised control trials comparing valved vs non-valved GDD viz. the Ahmed vs Baerveldt study (AVB study)[11] or the Ahmed Baerveldt Comparison study (ABC study)[12] have reported on mixed cohorts of primary and secondary glaucomas, a significant proportion of which had undergone previous trabeculectomy. However, the ABC study did stratify its cohort into four groups and demonstrated that the best results were obtained in the group of primary glaucomas which had undergone previous intra-ocular surgery and the worst outcomes were seen in the neovascular group. The ABC study reported that the AGV group failed on IOP end points whereas the Baerveldt Glaucoma Implant (BGI) failed on safety endpoints. Pooled data from both the studies,[13] showed that the failure rate was 37% in the BGI group vs 49% in the AGV group at 5 years but both demonstrated that lower target IOP is achieved in the non-valved BGI group.

The AADI is very similar to the BGI 350 and in a study by Puthuran and colleagues reporting the intermediate outcomes[14] in AADI, the failure rate was 9.5% at year 1, 27.8% at 2 years, 38.9% at 3 years and 50.1% at 4 years.

The failure rate reported by Puthuran et al at year 2 is much higher than that
reported previously by Pathak Ray and colleague (13%)\[15\] as well as in this study too (10%). Puthuran et al have reported increased failure rate in primary (vs secondary) glaucomas perhaps due to the higher rate of previous filtration surgery, providing credence to the hypothesis that previous filtration surgery may be implicated in lower success rates in GDD surgery, as noted by several other authors too.\[1-4\]

Results in this study are similar to the pooled data from the ABC and AVB studies at the end of 5 years[13] which showed that non-valved surgery group produced a lower mean IOP on fewer medications, had lower failure rates than the AGV group. However, the BGI group carried a risk of hypotony which was not seen in this current study.

There are very few studies originating in India which have compared the non-valved Aurolab Aqueous Drainage Implant (AADI), with the valved AGV. We have previously reported the outcomes of the two in a mixed cohort of primary and secondary glaucomas at 1 year – 92.3% overall success in the AADI group and 80.5% was seen in the AGV group (p<.001).\[16\] Pandav et al,\[17\] also reported in a mixed cohort - overall success was 73.08% and 58.18% in the AADI and AGV groups respectively at 3 years. The corresponding overall success rates in the current study are 92% and 88% at 1 year and 82% and 62% at 3 years in the AADI and AGV groups respectively.

Where intra-ocular positioning of the tubes of either of the GDD was concerned, the first choice in pseudophakic and aphakic eyes (and in all those that had simultaneous cataract extraction) was in the CS.\[18\] Notably, 2
consecutive pseudophakic neovascular glaucoma eyes, with AC placement of tubes, showed progressive shallowing of the AC with progression of ectropion uvaeae, had to be re-sited in the CS. Following this set-back, the practice of CS placement was routinely adopted in all pseudophakes, aphakes and those combined with cataract surgery. However, in eyes that undergo simultaneous SFIOL, it may be better to place the tube in the AC rather than risk IOL tilt and subluxation and this is the authors preferred technique.[19] Placement of the tube in CS has several advantages – it helps to minimise tube-endothelial touch, endothelial cell loss,[20] subsequent corneal decompensation, and interventions related to it – tube trimming, tube repositioning, tube extender, corneal graft etc. The rate of corneal decompensation was low in this study and was less than 5%. The rate of corneal decompensation in a recent large retrospective cohort[21] of over 1600 eyes with GDD implantation was 5%, but it has been reported to be as high as 17%[22] and 19%.[23] Beatson et al[21] found, age, post-operative hypotony, tube-cornea touch, Fuchs and Irido-corneal endothelial (ICE) syndrome to be significant risk factors. The preferred option in ICE syndrome should be the CS as far as feasible which may help to postpone keratoplasty for a significant period, if not avoid it altogether, as notified in a previous case series.[24] Tube-cornea touch and subsequent adverse events can be avoided with a CS placement or even a placement in the posterior segment; however, the latter requires pars plana vitrectomy (PPV). None of the GDD surgeries in the current study were combined with pars plana vitrectomy (PPV) nor were any tubes placed in the posterior segment.

Another very important aspect of GDD implantation is the occurrence of the
hypertensive phase. It tends to occur early and with greater severity in the valved devices as it is hypothesized that the early access of the aqueous to the nascent bleb around the endplate in the early post-operative period allows pro-inflammatory cytokines and other ligands\textsuperscript{[25]} to set up a fibrotic response in the subconjunctival space. It is postulated that this thickens and forms encystment of the bleb lining leading to increased resistance and thus and increase in IOP occurs. The incidence of HTP in AGV has been reported variably in literature – Ishida and colleague reported 26\% and 35\% respectively in a White and African-American cohort\textsuperscript{[26]} 33\% was reported by Abe et al\textsuperscript{[27]} in a mixed racial cohort, 31.3\% was reported in a Korean population\textsuperscript{[28]} 41.1\% in an Egyptian population\textsuperscript{[29]} 58.3\%\textsuperscript{[16]} 41.8\%\textsuperscript{[17]} and 63.93\%\textsuperscript{[30]} in three different studies in the Indian population.

On the other hand, HTP occurs rather more infrequently and presents much later in AADI surgery, only after the occlusive suture autolyses, and has been reported to occur in approximately 20\% of eyes\textsuperscript{[10]} The incidence of HTP in the AADI group in this study was comparable.

In the pooled analysis of the AVB and ABC studies\textsuperscript{[13]} AGV had a significantly higher rate of HTP (60\%) when compared to BGI (20\%). Therefore, the results obtained in the current study are consistent and comparable with the rate of HTP in the valved as well as the non-valved GDD as reported in literature.

A recent strategy to minimise the hypertensive phase in AGV is the use of early aqueous suppression\textsuperscript{[31]} This therapeutic intervention was adopted uniformly in the AGV group and aqueous suppressants were commenced as
soon as the IOP was detected in the early teens. This has resulted only in a marginal improvement in the HTP rate in the AGV group in this study (50.8%) compared to previously reported (58.3%).[16] Predictably therefore it is this phase as well as the use of AGV implant itself that was found to be significant factors for failure.

Even though complications occurred more frequently in the AGV group (65.5% vs 38.9%), most of these in both the groups were transient and were managed conservatively. These rates are comparable to those reported by Pandav et al. in the AGV group (62.9%) but not in the AADI group (75.2%). Most notably, none of the eyes in this study had persistent hypotony related complications in the AADI group whereas Pandav et al have reported a rate of 3.5% in the AADI group and 0.5% in the AGV group. This difference in the AADI group between the 2 studies may be explicable by the fact that all the surgeries in this series were performed by a single surgeon. Though there is not much variability in the surgical technique for the performance of an AGV, considerable technical skill is required in the implantation of a non-valved implant and may differ from surgeon-to-surgeon based on their experience.

However, the interventions required for some of these complications are rather more comparable between the groups in both the studies - 24.5% in AGV vs 17% reported by Pandav et al[17] and 15.2% in the AADI group vs 16% reported by the same authors.[17] Level and years of experience of the surgeon can reduce complications and interventions for these. This is perhaps reflected in AADI implantation also - in a previous report by Pathak Ray and colleague, [8] rate of interventions was 30.7% (vs 15.2% in this study) whereas it remained comparable in AGV implantation in both the
studies. It may also be indicative of a reduced rate of interventions in primary implantation of non-valved surgery in secondary glaucomas. Nonetheless, this hypothesis can be proven only when a study is conducted inspecting primary and secondary implantation of AADI in secondary glaucomas.

Visual acuity was comparable between the groups, but 4 eyes had vision worse than >2 lines in the AADI group and 2 eyes in the AGV group; this difference was not significant. Only one eye developed no light perception (following endophthalmitis) in the entire cohort and this was in the AGV group.

The retrospective nature of the study meant that inevitably there was a selection bias, evident by the somewhat mismatched pre-operative etiological characteristics between groups; however pre-operative IOP and AGM did not differ. This limitation was partially overcome by the inclusion of consecutive eligible eyes with the surgery being performed by a single surgeon in both the groups, eliminating variability of surgical technique as a confounding factor. Another perceived limitation is the patchy availability of endothelial cell count pre-and-post operatively; therefore, this parameter could not be analysed in this study.

In conclusion both devices are efficacious and safe when implanted primarily in filtration-surgery-naïve eyes with secondary glaucoma. Nevertheless, IOP in AGV, the costlier of the two devices, is more likely to be controlled by AGM (with lifelong implication of cost), more likely to fail with greater incidence of hypertensive phase when compared to AADI. On the
other hand, AADI implant showed a higher rate of complete success with significantly lower IOP and requirement of fewer AGM with less frequent complications than AGV implant.

References:


25. Freedman J, Iserovich P. Pro-Inflammatory Cytokines in Glaucomatous Aqueous and Encysted Molteno Implant Blebs and Their Relationship to Pressure. Investigative Ophthalmology & Visual


Dr. Pragya Saini,
DO (MAMC), DNB, MNAMS, FICO, MRCSEd, FLVPEI (Oculoplasty Res.), FAEH (Oculoplasty, Orbit and Ocular Oncology)
Orbit, Oculoplasty and Ocular Oncology
Ocular Oncology Fellow, Moorfields eye hospital, London

UPDATE ON THE LONG-TERM OUTCOMES FOLLOWING THE MANAGEMENT OF INCOMPLETE PUNCTAL CANALIZATION

INTRODUCTION:
Incomplete punctal canalization (IPC) is a congenital lacrimal drainage disorder characterized by the presence of fibrovascular membranes over the puncta, which are believed to be due to failure of canalization of the most proximal lacrimal drainage pathway. This pathology was initially referred to using a plethora of terms ranging from punctal membranes to punctal atresia to punctal dysgenesis or, incorrectly, even agenesis. The term “incomplete punctal canalization” or IPC was introduced in 2013, with further classification into incomplete punctal canalization-external membrane variant and incomplete punctal canalization-internal membrane variety. The incomplete punctal canalization-internal membrane variety gives an impression of blurred punctal margins with complete obscuration of the opening by the membrane, which is present just within the margins. The
pars lacrimalis portion of the eyelid is normal, unlike that of punctal agenesis. The external membrane variant presents as a smooth, translucent membrane with or without a vessel traversing over the membrane’s surface, giving a false impression of punctal agenesis. Rarely, there could also be a balloon variant of the incomplete punctal canalization external membrane variant. A balloon variant of IPC is a form of external membrane where a dome-shaped elevation is seen in the punctal area, translucent, and relatively avascular. Anterior segment optical coherence tomography scan of the IPC demonstrates a hyperreflective membrane covering the punctal area in a table-top configuration with visible patent vertical canaliculus underneath. About 27% had associated lacrimal drainage pathway disorders like canicular stenosis and congenital nasolacrimal duct obstruction in the earlier study. The management of IPC is a simple membranotomy using a Nettleship’s punctal dilator. Any other associated lacrimal drainage pathway disorder is dealt with as per standard protocols. The authors have earlier shown a 91% functional success rates with this simple procedure over a 6-month follow-up period. This study aims to assess the long-term outcomes of membranotomy and adjunctive measures in patients with IPC.

METHODS:

A retrospective interventional study was performed of patients diagnosed with IPC during the period January 2015 to June 2020. Institutional ethics committee approval was obtained, and the study adhered to the tenets of the Declaration of Helsinki. Data collected on chart reviews include demographics, clinical presentation, laterality, type of IPC, associated
lacrimal anomalies, management modalities, and long-term outcomes. Clinical diagnosis was made on observation of the puncta under indirect illumination of a single slit beam focused just adjacent to the puncta. A high degree of suspicion is needed to diagnose this condition. On slit-lamp examination, a slight dimpling or greyish translucency is visible at the puncta site, medial to the meibomian gland orifices. The external membrane variant completely covers the punctal area, with the membrane giving a false appearance of punctal agenesis. There may or may not be a vessel traversing over the surface of the membrane. The internal membrane variant appears as blurred punctal margins with the vessel bayonetting over the membrane surface. The vertical canaliculus is not visualized. The rest of the eyelid architecture, especially the pars lacrimalis portion of the eyelid, appears normal. All patients who opted for surgery underwent membranotomy using Nettleship’s punctal dilator as per earlier published protocols. Following the membranotomy, the canaliculi, and the distal lacrimal drainage pathways were assessed by probing and irrigation. Associated lacrimal drainage pathologies were also assessed by the clinical examination and treated appropriately as per earlier described protocols. Anatomical outcomes were assessed by the punctal patency confirmed by the morphological features of the punctum and lacrimal irrigation. The functional outcomes were assessed by the fluorescein dye disappearance test and subjective resolution of epiphora.

RESULTS:

Ninety-eight puncta of 62 eyes of 46 patients with IPC were examined in the
The mean age was 12.5 years (range: 2–35 years) with a male to female ratio of 1:1. Epiphora was the presenting complaint in all the patients. However, those presenting with clear history of epiphora since birth amounted to 32 patients (70%), and the rest noticed it within the first 3 years after birth. Bilateral involvement was seen in 35% of patients (16/46). All 4 puncta were involved in 16% of patients (7/46), and both upper and lower puncta of the same eye were involved in 34 eyes (55%). Lower puncta were marginally more involved (54%, 53/98) than the upper puncta (46%, 45/98). Incomplete punctal canalization- external membrane variants were noted in 62% (61/98) and the internal membrane variant in 38% (37/98). Seventy-eight puncta of 39 patients (79.5%, 78/98) underwent membranotomy using the Nettleship’s punctal dilator. Associated lacrimal drainage pathway deformities were seen in 31% of patients (12/39). Three puncta (4%, 3/78) in addition required mini-monoka stent insertion for partial canalicular obstruction (2.5%, 2/78) and canalicular stenosis (1%, 1/78). Five patients (13%, 5/39) had associated congenital nasolacrimal duct obstruction for which probing was performed under endoscopic guidance. Of these 5 patients, 3 patients required dacryocystorhinostomy for bony obstruction of the nasolacrimal duct (complex congenital nasolacrimal duct obstruction). A single patient had 3-wall canalicular hypoplasia (2.5%, 1/39). Associated punctal agenesis was noted in 3 patients involving the other punctum of the same eye (8%, 3/39). The mean follow-up duration was 28 months (12–60 months). Anatomical and functional outcomes were noted in 100% (39/39) and 97.4% (38/39) of the patients, respectively.

**DISCUSSION:**
Punctal membranes in children have been described earlier; however, the terminologies differ, and so also the management protocols. The paucity of knowledge of this condition is reflected in the lack of its understanding and subsequent management. In 2014, Ali et al. coined the term IPC to introduce uniformity and described the likely pathophysiology of IPC along with the associated lacrimal disorders and management protocols. The 6-monthly outcomes with membranotomy alone were very encouraging; however, the long-term outcomes of the procedure were not known. The present study described the anatomical and functional outcomes over a mean follow up of 28 months to be 100% and 97.4%, respectively, validating the earlier described management protocols. Associated lacrimal drainage disorders like congenital nasolacrimal duct obstruction (5/39, 13%) and canalicular pathologies (3/39, 8%) were also noted in almost similar proportions as mentioned in the study earlier.1 However, 2.5% (1/39) had canalicular wall hypoplasia, which was not seen in the earlier study. Three patients (8%, 3/39) also showed punctal agenesis involving the other puncta in the same eye. Familial associations of this condition have been described earlier. Although, the condition is rare, the authors could find one such familial association involving the mother and her 2 children in the series. However, the majority were sporadic with no familial association. Systemic associations, as seen in certain cases of punctal agenesis, were absent in IPC, although other lacrimal drainage pathologies have been found associated as described earlier. Other than these newer findings in the present study, the experience of nearly 7 years with IPC has provided newer insights. First, the membranotomy works best if the first puncture into the membrane is
performed with a fine dilator (one that rapidly tapers to a needlepoint), followed by a slow taper dilator (broad one). It is important to make sure the membranotomy is complete without any residual hanging membranes from anywhere circumferentially. The second meaningful learning was that IPC, unlike punctal agenesis, was not associated with any systemic disorders. The only exception was its rare occurrence in patients with congenital rubella syndrome. Third, following restoration of the anatomical patency in IPC, it is rare to encounter a functional failure. It could be possible that functional epiphora may represent accompanying incomplete maturation of the lacrimal pump or distal causes of a functional failure. However, this needs to be further studied. In conclusion, the present study validates the previously described protocols over a long-term follow-up. The study also emphasizes that more invasive approaches are not warranted for isolated cases of IPC. Patients with IPC demonstrate other lacrimal drainage anomalies associations. As shown in an earlier publication, familial association can exist; however, further studies with detailed genetic analysis would be required for demonstrating a genetic basis.
COMPARISON OF GLAUCOMATOUS FROM NON-GLAUCOMATOUS OPTIC NEUROPATHY USING OPTICAL COHERENCE TOMOGRAPHY.

Abstract:

The most common optic neuropathy worldwide is glaucomatous optic neuropathy (GON), but few non- glaucomatous optic neuropathies (NGON) also present with optic nerve head changes and visual field defects. Hence, distinguishing GON from NGON is a clinical challenge due to their management, systemic association and varied progression to visual morbidity. This retrospective study was conducted in 40 eyes, 20 with NGON and 20 with GON. All patients underwent a complete ophthalmic examination followed by radial Optical Coherence Tomography (OCT) optic disc scan to calculate Bruch's membrane opening minimum rim width (BMO-MRW). The 5-fold cross validated area under the curve for GON versus NGON from logistic regression models using BMO-MRW values from all sector was 0.95(95%CI : 0.86-1.00). The results showed that the values were significantly lower in GON than NGON group. Hence, OCT based BMO-MRW
values could be used as an objective tool to differentiate GON from NGON.

Introduction:

The most common optic neuropathy worldwide is Glaucomatous optic neuropathy (GON) presenting with optic nerve head changes and visual field defects. Non glaucomatous optic neuropathy (NGON) includes ischemic optic neuropathy, previous optic neuritis, compressive optic neuropathies, toxic or nutritional optic neuropathy and traumatic optic neuropathies which also present with optic nerve head changes along with visual field defects. Therefore, the diagnosis of NGON is often missed or misinterpreted as GON during ophthalmoscopic examination or by fundus photography assessment.[1] It is important to differentiate between GON and NGON because of the different management, systemic associations and visual impairment propensity is completely varied for each disease especially for compressive optic neuropathy (CON). Prompt and accurate diagnosis of CON is critical as it can be life threatening.[2] Previous studies have reported 6.5% of patients having intracranial compressive lesions involving anterior visual pathways who were previously diagnosed with normal tension glaucoma (NTG). Only 21% CON was correctly diagnosed by ophthalmologists by viewing fundus photographs.[3] The cup size assessment is challenging in most cases due to the arbitrary reference plane distinguishing the rim from the cup. Elevated intraocular pressure (IOP) is a risk factor for GON but not useful for differentiating between GON and NGON. A recent report suggested that newly diagnosed GON had IOP <22 mm of Hg in 50% of US population and 92% of Japanese population. [1] Hence, there is a need to develop
objective measurement to aid in differentiating GON from NGON in patients with optic nerve disease. Both GON and NGON show decrease in diameter of retinal arteriole and loss of retinal nerve fibre layer (RNFL) and hence doesn’t differentiate between GON and NGON.[4] Optical Coherence Tomography (OCT) is a novel, non-contact, non-invasive technique that allows cross sectional imaging of the anterior and posterior eye segment.[5] The recent description of the measurement of the minimum rim width at Bruch’s membrane opening (MRW-BMO) is said to provide an objective measurement of cupping. The aim of this study was to differentiate GON from NGON patients on the basis of MRW-BMO measurements.

**Material and Methods:**

Subjects were enrolled consecutively into a diagnostic evaluation study using area under the curve analysis (AUC) recruited a tertiary eye hospital in South India. The study was conducted according to the tenets of declaration of Helsinki. An ethics committee approval was obtained for this review. An informed consent was taken from all patients. Inclusion criteria included patients with pale disc who had their diagnoses confirmed based on characteristic optic disc appearance with matching glaucomatous visual field loss. IOP always below 21 mm Hg, and patients with open drainage angles on dark room gonioscopy. Exclusion criteria included Secondary glaucoma such as pseudo-exfoliation and pigment dispersion syndrome, age younger than 18 years, significant media opacity, clinical evidence of diabetic retinopathy, and macular degeneration or any other retinal disease, any participants unable or unwilling to undergo magnetic resonance
imaging (MRI) of the brain and orbits with contrast, IOP >21 mm Hg, narrow drainage angles, or a known family history of glaucoma. NGON was diagnosed by a neuro-ophtalmologist. Non-arteritic anterior ischemic optic neuropathy required previously documented painless disc swelling with visual field defects that either improved or stabilized over a 6-week period and a “disc at risk” in the contralateral eye. Prior optic neuritis was diagnosed based upon a clinical history consistent with optic neuritis and a contrast-enhanced MRI demonstrating optic nerve enhancement during the symptomatic phase of the patient. All subjects underwent a complete ophthalmic examination including best-corrected visual acuity, near vision, colour vision (Ishihara plates), IOP with Goldmann applanation tonometry, Humphrey visual field and OCT [Heidelberg Engineering, Heidelberg, Germany] BMO-MRW. All GON patients underwent MRI of the brain and orbits with gadolinium enhancement using a standard protocol. The OCT was performed by a trained technician. The scanning protocols for the OCT followed previously published protocols. Briefly, the BMO-MRW scanning pattern is a radial scan consisting of 24 equally distributed high-resolution 15-degree B-scans which compute the neuro-retinal rim measurements centred on the optic nerve head. The BMO-MRW scan was segmented into 6 sectors (temporal, nasal, superotemporal [ST], inferotemporal [IT], superonasal [SN], and inferonasal [IN]). The BMO was manually marked by a single clinician. Only 1 eye for each patient was included in the study. If both eyes were eligible, the worst affected eye was included for analysis.

Statistical Analysis:
All statistical analysis were performed using univariate logistic regression model in order to assess the association between MRW-BMO and the presence of GON. The predictive value to classify GON and NGON was done by 5- fold cross validated logistic regression model to calculate AUC, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and likelihood ratios. The positive likelihood ratio (PLR) was calculated as sensitivity/ (1-specificity), and the negative likelihood ratio (NLR) was calculated as the (1-sensitivity)/specificity. A higher PLR (>1) gives an increased probability of having a disease following a positive test result, whereas a lower NLR (between 0 and 1) gives a lower probability of having a disease following a negative test result. MRW-BMO was calculated for 1) all sectors, 2) ST and IT sectors 3) SN and IN sectors 4) ST, IT and temporal sector 5) SN, IN and nasal sectors. All analyses were conducted using R version 3.5.1 software (R Project, Vienna, Austria) with the caret application (Version 6.0-80) for cross-validation of logistic regression models and the pROC application (version 1.13.0) for plotting receiver operating characteristic (ROC) curves.
<table>
<thead>
<tr>
<th></th>
<th></th>
<th>GON (n=20)</th>
<th>NGON (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Gender</td>
<td>Male</td>
<td>10 (50.0)</td>
<td>13 (65.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td>10 (50.0)</td>
<td>7 (35.0)</td>
</tr>
<tr>
<td>2</td>
<td>Laterality</td>
<td>Right Eye</td>
<td>12 (60.0)</td>
<td>11 (55.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left Eye</td>
<td>8 (40.0)</td>
<td>9 (45.0)</td>
</tr>
<tr>
<td>3</td>
<td>Age</td>
<td>(Mean ± SD)</td>
<td>69.45 ± 1.55</td>
<td>58.5 ± 2.32</td>
</tr>
<tr>
<td>4</td>
<td>ST</td>
<td>129.65 ± 7.4</td>
<td>249.35 ± 15.3</td>
<td>0.0000</td>
</tr>
<tr>
<td>5</td>
<td>IT</td>
<td>169.55 ± 4.1</td>
<td>269.35 ± 12.3</td>
<td>0.0000</td>
</tr>
<tr>
<td>6</td>
<td>Temporal</td>
<td>168.4 ± 4.0</td>
<td>273.3 ± 11.8</td>
<td>0.0000</td>
</tr>
<tr>
<td>7</td>
<td>SN</td>
<td>224.25 ± 5.3</td>
<td>323.4 ± 21.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>8</td>
<td>Inferonasal</td>
<td>237.35 ± 6.0</td>
<td>304.75 ± 18.8</td>
<td>0.0015</td>
</tr>
<tr>
<td>9</td>
<td>Nasal</td>
<td>226.8 ± 6.4</td>
<td>343.2 ± 23.1</td>
<td>0.0000</td>
</tr>
</tbody>
</table>
Mean values ± standard deviation of ONH values with OCT

Results:

40 patients were recruited. This included 20 patients with GON and 20 patients with a range of other optic neuropathies including ischemic (9), previous optic neuritis (3), compressive (3), toxic/nutritional (3) and traumatic (2). The mean age was $69.45 \pm 1.55$ for GON patients and $58.5 \pm 2.32$ for NGON patients. The MRI scan reports for the compressive optic neuropathy patients showed findings suggestive of meningioma. All GON patients had a normal MRI brain and orbits with gadolinium, as assessed by a specialist neuro-radiologist. Mean MRW-BMO measurements were taken. The BMO-MRW in the GON group were significantly lower than the NGON group. The models using all the sectors had mean AUC using the BMO-MRW
values 0.95 [95% confidence interval [CI]: 0.86-1]. Sensitivity calculated was 100% with a corresponding specificity of 95%. The model using superonasal, inferonasal and nasal sectors had the highest PLR (9 [95% CI]).

<table>
<thead>
<tr>
<th>Model</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>LRP</th>
<th>LRN</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Sectors (ST, IT, SN &amp; IN)</td>
<td>100.00</td>
<td>95.00</td>
<td>95.24</td>
<td>100.00</td>
<td>2.00</td>
<td>0.00</td>
</tr>
<tr>
<td>ST &amp; IT sectors</td>
<td>100.00</td>
<td>95.00</td>
<td>95.24</td>
<td>100.00</td>
<td>2.00</td>
<td>0.00</td>
</tr>
<tr>
<td>SN &amp; IN sectors</td>
<td>100.00</td>
<td>85.00</td>
<td>86.96</td>
<td>100.00</td>
<td>6.67</td>
<td>0.00</td>
</tr>
<tr>
<td>ST, IT and Temporal</td>
<td>100.00</td>
<td>100.00</td>
<td>100.00</td>
<td>100.00</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SN, IN and Nasal</td>
<td>90.00</td>
<td>90.00</td>
<td>90.00</td>
<td>90.00</td>
<td>9.00</td>
<td>0.11</td>
</tr>
</tbody>
</table>
1. SN & IN

2. ST & IT:

3. ST, IT & Temporal

253
Discussion:

The study demonstrates that MRW-BMO provides a good objective differentiation between the 2 groups in tightly phenotypic clinic-based populations of GON and NGON. Glaucoma refers to retinal ganglion cell death and the complex interplay of biochemical factors related to glaucoma comprising of ischemia, physical compression of axonal bodies and tissue remodelling. The hallmark of glaucoma is optic nerve head cupping which refers to laminar or deep cupping to distinguish it from other types of non-glaucomatous cupping.[1] Previous reports have suggested that glaucomatous cupping has a greater anterior laminar depth than non-glaucomatous cupping.[2] NGON including arteritic ischemic optic neuropathy, dominant optic atrophy and few compressive optic neuropathies show non-glaucomatous cupping.[5] GON being a more common pathology and with cognitive biases would mean that an abnormal disc and visual field is more readily considered as signs of glaucoma, without the considerations of other possible pathologies. OCT is a routine investigation in most high resource centres for assessment of glaucoma patients and hence MRW-BMO could be included as a routine investigation through the OCT platform. Chauhan et al. could prove that BMO-MRW had a better diagnostic performance compared with current confocal scanning laser tomography or other SD-OCT–based ONH and RNFL parameters.[6] The possibility of NGON could alert the clinician for prompt treatment and need for other investigations like MRI scan, colour vision, reassessing visual fields or re-examination of the disc to consider the evaluation of pallor rather than cupping. These results only help in differentiating GON from NGON but do
not provide any aid in subtyping the specific NGON which have been presented. Larger study samples for less common NGON like hereditary optic neuropathies and CON may help to identify characteristic OCT findings that may assist in differentiating each of these conditions from glaucoma which is a big challenge otherwise. The current clinical limitation of detecting NGON by clinicians is that they may not even consider it.

In conclusion this study has highlighted a practical method of assessment besides presenting aspects of the pathogenesis of glaucomatous optic neuropathy. It may lead to a rediscussion as to whether patients with the ophthalmological diagnosis of normal-pressure glaucoma need a neuroradiological examination. Objective assessment of optic head cupping with MRW-BMO measurements in OCT helps to differentiate GON from NGON.

References:


Dr. SWATI PHULJHELE
Additional Professor
Neuro-ophthalmology and Strabismus Services
Dr Rajendra Prasad Centre for Ophthalmic Sciences
All India Institute of Medical Sciences, New Delhi.

EVALUATION OF OCT – ANGIOGRAPHY CHANGES IN NON-ARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY

Purpose:

To study the long-term microvasculature changes at macula and the optic disc in eyes with non-arteritic anterior ischemic optic neuropathy (NAION).

Methods:

Patients with acute NAION of less than 6 weeks duration were included. Optical coherence tomography angiography (OCTA) of the macula and the optic disc were performed at baseline, 3 and 6 months and compared with the controls.

Results:

The mean age of 15 patients was 52.25 (± 9.06) years. The whole image superficial, peripapillary and radial capillary densities were progressively decreased at 3 & 6 months (P<0.05). There was decrease in superficial
capillary plexus (SCP) at macula at presentation.

Conclusions:

In a 6 months observation of acute NAION eyes, the peripapillary capillary densities show progressive loss.

Introduction

Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION) is the commonest acute optic neuropathy above the age of 50 years\(^1\). The underlying pathology in case of NAION is vascular insufficiency in the optic nerve head (ONH), secondary to a fall in perfusion pressure in posterior ciliary Arteries\(^2\). Several modalities like; fluorescein angiography, indocyanine green angiography and doppler have been used to study the vascular pattern of disc in cases of NAION however none of them could detect the vascular pattern at different layers. Optical Coherence Tomography- Angiography (OCT-A) is a non-invasive modality, that allows visualisation of retinal vasculature at different levels. The pattern of microvascular loss, can help in understanding the anatomical basis of pathological process.

Studies have documented presence of vascular loss increase in non-perfusion area on OCTA in NAION patients when compared to control eyes in both acute and chronic phase.\(^3\)\(^-\)\(^7\) OCTA has also been used to differentiate NAION from papillitis and papilledema.\(^5\)\(^,\)\(^8\) Fard MA et al \(^8\) found reduced peripapillary microvascular density in acute cases as compared to acute
papillitis and papilledema cases, and found no reduction in papilledema, in contrast to papillitis that showed similar reduction in density as NAAION. Few studies have evaluated the choroidal vasculature in NAION patients with variable results. U Gandhi et al 5 found 2 distinct patterns of microvasculature loss at choroidal level – diffuse loss of peripapillary cuff (in all the patients), and sectoral loss of vasculature (57.14% of patients) in acute cases. Wright Mayes E et al 3 in their retrospective, cross-sectional study of 10 eyes described qualitative alterations in peripapillary vasculature, at the level of radial peripapillary capillary (RPC) and choriocapillaris (PCC). Dhiman R. et al 9 in their series of 10 eyes in non-acute phase found significant difference in superficial microvascular density around the disc. However, at the level of choroid, the difference was not significant.

Moreover, the macular plexus has also been shown to have vascular changes in cases of NAION. Z Y Tao et al 10 and Augstburger E et al 11 found reduced density in superficial plexus and both superficial and deep plexus layer respectively, at macula. On the other hand, Chun-Hsiu Liu et al 12,13 did not find a significant decrease in macular density in chronic stage.

This loss of vascular plexus at disc, peripapillary area and macula could be the cause or the consequence of the ischemic pathology of NAION. This study aims to evaluate the natural course of the pattern of the vascular loss around disc and at macula.

Materials & Methods

This was a prospective, observational longitudinal study conducted over a
period of two years at a tertiary eye care centre. Institute ethical clearance was obtained, and the study followed the tenets of the declaration of Helsinki.

Patients presenting to the neuro-ophthalmology clinic of our centre were evaluated, and after the fulfilment of inclusion criteria were enrolled in the study. Informed consent was obtained from all the participants of the study.

The patients of diagnosed as unilateral NAION based on clinical features; age 40-80 years, unilateral acute painless visual loss associated with swollen disc, presence of relative pupillary defect; presenting within 6 weeks of onset of symptoms. Patient underwent ESR, CRP to rule out arteritic AION. The exclusion criteria included all other optic neuropathies ruled based on visual field (whenever possible) and neuro-imaging (whenever indicated). Presence of glaucoma or other causes of retinopathy (except grade 1 hypertensive retinopathy), intraocular surgery (except cataract surgery) and myopia of >6D was excluded. The fellow eyes of these patients were also included in the study.

Healthy, age matched controls were included if they had a normal fundus examination, refractive error between +5 to -5 Dioptries, normal intraocular pressure (< 21 mm hg), no visual field defect, normal RNFL and GCL thickness, open angle on gonioscopy, and no previous history of ocular surgery (except uncomplicated cataract surgery with a posterior chamber intraocular lens).

The 15 eyes of 15 age matched control were also recruited.

Patients and control underwent complete ocular examination, visual acuity
assessment on logMAR chart and OCTA. The enrolled patients were followed up twice, at 3 months and 6 months from first presentation and OCTA was done on each follow up visit.

All patients and controls underwent SS-OCT-A on the Topcon Swept Source DRI OCT Triton™ (TOPCON MEDICAL SYSTEMS, INC). The scans are performed utilizing a 1050 nm wavelength light source, and a scan speed of 100,000 A-Scans per second. The higher wavelength provides deeper penetration and less light scattering. The 1,050nm light source is invisible to the human eye, and allows fixation of the patients on the provided target.

The scans were performed at macula and at optic disc (4.5 mm x 4.5 mm). All scans were performed by an experienced operator. The patients underwent pupillary dilation with 1% tropicamide drops prior to the exam. The scans that had an image quality >50 was included for the study. In case of motion artifacts and poor fixation the scans were repeated till a satisfactory scan was acquired.

Automated segmentation of layers was done, as provided by the device. The segmentation was manually adjusted in case of optic disc edema that interfered in automatic segmentation of vascular slab. The macular scans did not require manual adjustment.

The enface images for macular scan were at the level of superficial plexus, deep plexus and choriocapillaris; ONH scan enface images were segmented at ONH, radial peripapillary capillary layer and choriocapillaris layer. These were automatically defined by the ImageNet 6 software.

All retrieved images were processed using the ImageJ software (National
Institutes of Health, Bethesda, Maryland). This was done to quantitatively measure the microvascular density at various levels. The images were first converted to 8-bit image to enable application of thresholding algorithm. In peripapillary scans, the first step was to remove the large vessels in the image to accurately isolate the microvascular network. This was achieved by applying “Minimum” auto global thresholding algorithm that resulted in an outline of only the major vessels, in a binarized image that showed them as white lines on a black background (figure 3). Using the histogram option, the number of pixels that were white (represented as 255 in the histogram list) was noted. The enface image was now opened in another window and subjected to the Phansalkar's local thresholding algorithm. Phansalkar is a local auto thresholding algorithm that is well suited for low contrast settings. It was originally described for use in cytological analysis and is a modification of Sauvola's local thresholding method. Using the histogram analysis, the number of white pixels were again noted and the white pixels calculated from prior global thresholding, that represented large vessels, were subtracted from this. Lastly, the ratio of this corrected value of white pixels to the total number of pixels was calculated, and this was recorded as whole image microvascular density (in %). This method of removal of large vessels was necessary at superficial macular plexus, at ONH superficial plexus and at radial peripapillary capillary layer.

The above method yielded microvascular densities (%) at various levels, which were recorded and compared over subsequent visits. In the peripapillary scans, microvascular density was recorded at superficial (ONH) level, at the level of radial peripapillary network and the level of
choriocapillaris. Similarly, in macular scans, the microvascular density was recorded at superficial capillary plexus, deep macular capillary plexus and at the level of choriocapillaris. The final parameters used for statistical analysis were following:

- Whole image superficial peripapillary density (wiSPD)
- Whole image radial peripapillary capillary density (wiRPC)
- Whole image peripapillary choriocapillaris density (wiPCC)
- Whole image superficial macular density (wiSMD) at the level superficial plexus
- Whole image deep macular density (wiDMD) at the level deep plexus
- Whole image macular choriocapillaris density (wiMCC) - at the level of choriocapillaries

All observational data was compiled into an excel sheet, and statistical analysis was done using IBM Statistical Package for Social Science (SPSS) Statistics version 27. Inter-group analysis was performed using independent samples T- test for parametric values and Two- sample Wilcoxon rank-sum (Mann-Whitney) test for non- parametric values; for intra-group analysis paired sample T- test and Wilcoxon sign-ranked test was conducted. A p value of < 0.05 was considered as significant.

**Results**

This study recruited 15 eyes of 15 patients with acute NAAION (defined as < 6 weeks from onset). 3 patients could not follow up at 6 months owing to COVID-19 pandemic and hence were excluded from 6-month analysis. The
mean time of presentation from onset of symptoms was 3.89 weeks ± 1.69.

**Table 1 gives the demographic details of the patients.**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients</th>
<th>Control</th>
<th>p =</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>52.25 ± 9.06</td>
<td>52.66 ± 9.37</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Male: Female</td>
<td>10:5</td>
<td>8:7</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>LogMAR BCVA</td>
<td>1.0928 ± 0.63</td>
<td>0.00</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Seven patients had hypertension. Out of these, one patient was also suffering from coronary artery disease, while two had controlled type II DM. Two patients were suffering only from type II DM and had adequate glycemic control on oral medications. Three patients were found to have raised homocysteine levels on evaluation; there were no other systemic abnormalities detected in them.

**Swept Source OCT- A parameters**

**Peripapillary microvasculature assessment**

Whole image superficial (ONH) peripapillary density (wiSPD): At presentation the mean wiSPD in the affected eyes was 42.49 ± 5.28. The density was significantly reduced when compared to controls 46.36 ± 2.09 (Table 2) p value = 0.015, which reduced further at 3 months and 6 months. (Table 3)

Whole image radial peripapillary capillary density (wiRPC): At presentation the mean wiRPC in the affected eyes was 49.35± 5.64. The density was significantly reduced when compared to controls, 53.45± 1.96 (Table 2) (p
Further significant reduction in the density was seen on subsequent follow up (Table 3).

Whole image peripapillary choriocapillary density: The mean wiPPC in the affected eyes at presentation was 55.23±4.51. The density was significantly reduced when compared to controls 60.60±3.17 (Table 2). However, it showed significant improvement at 3 months and stabilized thereafter at 6 months. (Table 3)

Table 2 shows the comparison of various peripapillary vasculature parameters between the NAION eyes at presentation and control eyes.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>NAION (n=15)</th>
<th>Control (n=15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>wiSPD</td>
<td>42.49 ± 5.28</td>
<td>46.36 ± 2.09</td>
<td>0.015</td>
</tr>
<tr>
<td>wiRPC</td>
<td>49.35±5.64</td>
<td>53.45±1.96</td>
<td>0.012</td>
</tr>
<tr>
<td>wiPCC</td>
<td>55.23±4.51</td>
<td>60.60±3.17</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 3: Trend of change in peripapillary vasculature in NAION eyes. The p value provided is for change from respective previous value for each parameter.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline (n=15)</th>
<th>At 3 months (n=15)</th>
<th>At 6 months (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(in Mean ±)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

265
<table>
<thead>
<tr>
<th>wiSPD</th>
<th>wiRPC</th>
<th>wiPCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>42.49 ± 5.28</td>
<td>49.35 ± 5.64</td>
<td>55.23 ± 4.51</td>
</tr>
<tr>
<td>36.58 ± 3.29</td>
<td>44.64 ± 4.2</td>
<td>59.219 ± 3.19</td>
</tr>
<tr>
<td>(p=&lt; 0.001)</td>
<td>(p=&lt; 0.001)</td>
<td>(p=&lt; 0.03)</td>
</tr>
<tr>
<td>35.66 ± 2.93</td>
<td>43.99 ± 4.78</td>
<td>60.48 ± 2.73</td>
</tr>
<tr>
<td>(p=&lt; 0.001)</td>
<td>(p=&lt; 0.02)</td>
<td>(p=&lt; 0.2)</td>
</tr>
</tbody>
</table>

2) Macular microvasculature assessment

Whole image superficial macular density (wiSMD): At presentation the mean wiSMD in affected eyes was 41.83 ± 3.64. The density was significantly reduced when compared to controls 47.30 ± 2.04 (Table 4). It remained stable at 3 and 6 months although still significantly less than the control group. (Table 5)

Whole image deep macular density (wiDMD): At presentation the mean wiDMD in affected eyes was 52.15 ± 4.84. The density was significantly reduced when compared to controls 55.13 ± 1.81. (Table 4). There was no significant subsequent change on 3 & 6 month follow up visit and remained significantly less than controls. (Table 5)

Whole image macular choriocapillary density (wiMCC): At presentation the mean wiMCC in the affected eyes was 62.10 ± 5.95. The density was not significantly different from the control group 62.48 ± 2 (Table 4). No further change was seen in wiMCC on subsequent follow and it remained at par with
the control group. (Table 5)

Table 4 shows the comparison of various macular vasculature parameters between the NAION eyes at presentation and control eyes.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>NAION (n=15)</th>
<th>Control (n=15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>wiSMD</td>
<td>41.83 ± 3.64</td>
<td>47.30 ± 2.04</td>
<td>0.001</td>
</tr>
<tr>
<td>wiDMD</td>
<td>52.15 ± 4.84</td>
<td>55.13 ± 1.81</td>
<td>0.035</td>
</tr>
<tr>
<td>wiMCC</td>
<td>55.23 ± 4.51</td>
<td>60.60 ± 3.17</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Table 5: Trend of change in macular vasculature in NAION eyes. The p value provided is for change from respective previous value for each parameter.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline (n=15)</th>
<th>At 3 months (n=15)</th>
<th>At 6 months (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(In Mean ±</td>
<td>42.03 ± 3.3</td>
<td>42.88 ± 2.93</td>
</tr>
<tr>
<td></td>
<td>SD)</td>
<td>(p &gt; 0.05)</td>
<td>(p &gt; 0.05)</td>
</tr>
<tr>
<td>wiSMD</td>
<td>41.83 ± 3.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>wiDMD</td>
<td>52.15 ± 4.84</td>
<td>51.67 ± 3.37</td>
<td>52.43 ± 3.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(p &gt; 0.05)</td>
<td>(p &gt; 0.05)</td>
</tr>
<tr>
<td>wiMCC</td>
<td>62.10 ± 5.95</td>
<td>62.42 ± 5.76</td>
<td>60.48 ± 2.73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(p &gt; 0.05)</td>
<td>(p &gt; 0.05)</td>
</tr>
</tbody>
</table>
Discussion

The pathogenesis for NAION was described by Hayreh utilising fluorescein angiography who suggested that the transient hypoperfusion of ONH leads to neuronal ischemia, and consequently neuronal death. The vascular basis of pathology, though firmly established, however was still not discerned at the microvascular level owing to a lack of modalities that could study them. With the advent of optical coherence tomography-angiography (OCT-A), a detailed analysis of retinal and choroidal microvasculature is possible. OCT-A also provides a quantitative assessment of microvasculature that makes is more objective evaluation.

Multiple OCTA machines and their built-in proprietary software give quantitative measures of microvascular density [e.g., Cirrus (AngioPlex software, Carl Zeiss Meditec, Inc., Dublin, CA, USA), AngioVue software (Optovue, Inc., Fremont, CA, USA), RS-3000 Advance (Nidek, Gamagori, Japan), and OCTARA (Topcon Corporation, Tokyo)] have been noted to have good repeatability between tests. In platforms where proprietary software is not available, or where further refinement in density measurement is essential, images are exported and processed by variety of thresholding algorithms, using another software (for example, ImageJ - NIH, Bethesda, MD).

Rabiolo et al compared various methods to quantify microvascular density in macular and peripapillary area using OCT-A. They concluded that absolute density values are not interchangeable between different methods, and hence normative database for one method cannot be compared with
other. The longitudinal monitoring of vessel density however, can be achieved using the same algorithm if same instrument with same scan pattern and location is used.

The aim of this study was to evaluate longitudinal changes occurring in microvascular density in the peripapillary and macular vascular plexuses, over the course of 6 months using OCT-A, to understand the natural history of the NAION. The follow up studies on OCTA may help in understanding the natural history of NAION. Study of parafoveal vasculature by OCT-A explores the effect of NAION on macular vasculature, as well as further evaluates the possibility of a separate microvascular insult leading to macular thinning observed in NAION.

Fifteen eyes of 15 patients that presented with NAION presenting within < 6 weeks from symptom onset, were included in the study. Three patients could not follow up at 6 months owing to COVID-19 pandemic and hence were excluded from the analysis at 6 months. Fifteen age matched controls were also included in the study.

All patients and controls underwent SS-OCT-A on the Topcon Swept Source DRI OCT Triton™ and microvascular plexuses as segmented by the device were individually evaluated for longitudinal changes over the course of 6 months. To study differences at each plexus level, all scans were exported from the device and processed with ImageJ software using Phansalkar algorithm (as described in methodology). ImageJ was preferred over automated software, as we can selectively eliminate the larger vessels in the scans which enables us to accurately measure the microvascular density, as
reported by Dhiman et al\textsuperscript{9}.

In the peripapillary scans, our study conclusively shows a significantly low microvascular density at all levels studied (superficial (ONH), radial peripapillary capillary, choriocapillaris) at presentation when compared to control group. The reduction in peripapillary retinal microvasculature in NAION, as noted by us, replicates the findings of previous studies\textsuperscript{3-9}. The RPC layer, as described by Michaelson\textsuperscript{16} and Henkind\textsuperscript{17}, is derived primarily from parapapillary retinal arterioles and forms a network within the RNFL layer that runs parallel to the axons and acts as the primary supply to the axons. As reported from few studies\textsuperscript{18,19}, central retinal vasculature is not the sole contributor to the RPC layer and short posterior ciliary arteries do contribute via anastomosis. As the primary insult in NAION is a transient hypoperfusion of posterior ciliary arteries, this may contribute to the RPC density reduction. In addition, a direct insult to the ONH in NAION results in axonal swelling, that sets up a cycle of compression of central retinal microvasculature that further contributes to ischaemia and resultant swelling. The choroidal filling defects are primarily seen in arteritic forms of AION, but they have been demonstrated in non-arteritic form also \textsuperscript{20-22}. However, it should be noted in the acute setting where there is optic nerve head and RNFL edema, there is a high propensity for segmentation errors and loss of signal from underlying choriocapillaris that may lead to false low values.

On follow up of the study group, the peripapillary retinal microvasculature showed further drop in density. This reduction in microvasculature is likely a consequence of RNFL atrophy, that leads to a reduced metabolic demand
and hence a rarefaction of the capillaries. At the level of peripapillary choriocapillaris, OCT-A revealed that the density returned to the level of controls and there was no significant difference between the two groups at 3 months and 6 months of follow-up. As mentioned previously, the initial transient reduction in choriocapillaris density followed by resurgence to normal levels could be a consequence of transient hypoperfusion in acute cases or simply an artifact of loss of underlying signal due to ONH oedema.

The assessment of microvasculature at the macula was done at superficial macular capillary plexus (SMD) and deep macular capillary plexus (DMD) and choriocapillaris (MCC). We found significant reduction in the SMD at presentation, from the control group. However, there was no significant change seen in the microvascular density at superficial level at 3 months and 6 months. At the level of deep plexus, the microvascular density was significantly reduced when compared to controls. This also did not show any significant change over the course of 6 months. The reduction in retinal microvasculature in NAION may seem counter-intuitive, considering that posterior ciliary arteries, which are the primary site of hypoperfusion in NAAION do not contribute to superficial and deep macular plexus. The secondary ganglion cell loss (GCC) that occurs in NAAION may represent the sole reason for reduced superficial density, as these capillaries nourish the GCC and reduces in response to reduced metabolic demand. In addition, there is a possibility that swelling at ONH may compress retinal microvasculature leading to decreased density at both superficial and deep layers at the macula. Fard MA et al\textsuperscript{23} and ZY Tao et al\textsuperscript{11} both found reduced density only at the superficial level, thus affirming that the macular vessel
density loss is secondary to GCC atrophy; Augstburger et al\textsuperscript{10} found reduced density at both superficial and deep levels, hinting at the component of retinal ischemia also. At the level of macular choriocapillaris, no change was seen between the groups. As the alteration in chorioidal flow occurs only in peripapillary choroid in NAAION, this was an expected finding and discards any role of chorioidal vasculature disturbance in macula.

To conclude, our study shows a decrease in peripapillary retinal microvasculature in NAION, that reduces further over 6 months as neuronal atrophy sets in. Macular microvasculature shows conclusive reduction in early stages, that remains stable through 6 months; the changes are definite at superficial level but changes at deep macular plexus may require further studies with adequate matching for validation.

The major limitation of this study is small sample size. And the fact that in the acute phase of NA-AION, the segmentation at ONH is prone for error due to oedema that distorts the anatomy, leading to potential errors in measurement. Nonetheless the study demonstrates that OCT-A in NAION can be useful in detecting microvasculature alterations occurring in the ONH and macula.

References


7. Wang YH, Ma J, Gan LY, et al. optic nerve morphology and vessel density in eyes with different phases of non-arteritic anterior ischemic optic neuropathy. Zhonghua


ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING IN OCULAR ONCOLOGY: RETINOBLASTOMA

Abstract:

Purpose:

To explore the utility of AI and machine learning in the diagnosis and grouping of intraocular retinoblastoma (iRB)

Methods:

AI and Machine learning, Computer Vision (OpenCV)

Results:

Of 771 fundus images of 109 eyes, 181 images had no tumor and 590 images displayed iRB based on review by 2 independent ocular oncologists (with an inter-observer variability of <1%). The sensitivity, specificity, positive predictive value, and negative predictive value of the trained AI model was 85%, 99%, 99.6%, and 67% respectively. Of 109 eyes, the sensitivity, specificity, positive predictive value, and negative predictive value for
The detection of RB by AI model was 96%, 94%, 97%, 91% respectively. Of these, the eyes were normal (n=31) or belonged to group A (n=1), B (n=22), C (n=8), D (n=23), and E (n=24) RB based on review by 2 independent ocular oncologists (with an inter-observer variability of 0%). The sensitivity, specificity, positive predictive value, and negative predictive value of the trained AI model was 100%, 100%, 100%, and 100% for group A; 82%, 98%, 90%, and 96% for group B; 63%, 99%, 83%, and 97% for group C; 78%, 98%, 90%, and 94% for group D, and 92%, 91%, 73%, and 98% for group E respectively.

**Conclusion:**

The AI model for iRB is highly sensitive in detection of RB with high specificity for classification of iRB.

**Introduction**

The concept of artificial intelligence (AI) dates back to 1950 and is based on Alan Turing’s experiment on imitation game,[1] though the term AI was coined by John McCarthy in 1956 at the Dartmouth Summer Research Project on AI. The use of AI in medicine has gained importance in the past few decades. AI in medicine is either in virtual form via machine learning (ML) or deep learning aiding in the development of complex treatment algorithms, predictive models via electronic medical records and big data, or softbots;[2,3] or physical form via sophisticated medical devices and robots or carebots.[2,4]

In the virtual form, there have been various applications of AI and ML in the field of medicine mainly based on numerical data and digital images. The
Various applications in medicine include use of epidemiology informatics in public health,[5] improvement of decision making in anaesthesiology,[6] improvement of precision medicine in the fields of reproductive medicine[7] and cardiovascular medicine,[8] improvement of diagnostic accuracy and objectivity in pathology with the advent of digital pathology,[9] improvement of technological aspects, image quality and image reading in nuclear medicine,[10] and also aiding in diagnosis, evaluation of prognosis, prediction of epidemic, and drug discovery in the recent COVID-19 pandemic.[11] In the field of cancer, AI and ML has contributed to image analysis, improving diagnosis, multi-layered data analysis with integration of cancer genomics, development of treatment algorithms, estimating prognosis, drug discovery, and ultimately improving the cancer healthcare to precision oncology.[12]

In the recent years, there has been increasing interest for the use of AI and ML in the field of ophthalmology. Ophthalmology is a branch of medicine which uses various imaging modalities such as fundus photographs, optical coherence tomography, computed tomography, magnetic resonance imaging etc; and is based on numerical data such as visual acuity, intraocular pressure, corneal thickness, refractive error, cup to disc ratio etc for diagnosis and prognosis of various ophthalmic diseases. Numerical data and digital images have been used to develop AI and ML models for various diseases in ophthalmology. Till date, there have been no AI models for the diagnosis of retinoblastoma (RB) and herein, we explore the utility of AI and ML for diagnosis and classification of intraocular RB.

**Methods**
This was a retrospective study conducted at the Operation Eyesight Universal Institute for Eye Cancer, LV Prasad Eye Institute, Hyderabad, India and TechSophy, Hyderabad, India. Approval from the Institutional Review Board was obtained. The study adhered to the tenets of Declaration of Helsinki. Fundus photographs of children diagnosed with treatment-naïve unilateral or bilateral RB from January 2017 to June 2021 were retrieved from the institutional database. All images were captured on Retcam II (Clarity Medical Systems, Inc., Pleasanton, CA, USA). Poor quality images were excluded. All images were read by two independent ocular oncologists (VSV, NG) and labelled as normal or RB. In images with tumors, a group label was assigned to every image according to the International Classification of Intraocular Retinoblastoma (ICIoR) as Group A, B, C, D, or E. After reviewing all images of a single eye, a cumulative label was assigned as Normal, Group A, B, C, D, or E. In cases of discrepancy of interpretation between the 2 ocular oncologists, label assigned by VSV was taken as the gold standard for comparison with the results from AI model.

The images that were manually labelled were also used to develop and test the AI model for RB by feature extraction and use of RB classifier. These are described in detail below:

**Feature extraction:**

The features needed for the classification of RB according to ICIoR were extracted using a series of algorithms that involved deep learning object detection, computer vision, and other geometry and intensity gradation algorithms. Open Computer Vision (OpenCV) techniques and deep learning
(DL) models were employed to extract, identify or calculate the following features from every image: hough circle (i.e. entire area of fundus captured within an image), optic disc (detection), tumor (detection), maximum tumor size (mm), number of tumors, distance between optic disc and the closest tumor, vitreous seeds, sub-retinal seeds, number of seeds, maximum distance between seeds and the nearest tumor, blood vessels and intraocular hemorrhage. Feature vectors representing the image were used to train the RB classifier of the AI model (Figure 1). Eighty percent of the images in the dataset were used to train the classifier and 20% were used to test the RB classifier.

For detection of optic disc and tumor, Multi-Label Classification Model of Deep Learning (DL) was utilized on training and test images to predict a bounding box and class with a confidence score for each prediction (Figure 2A and 2B). Transfer learning\cite{14} was used for training the AI model in identification of optic disc and tumor.

Transfer learning implementation used an efficient Mobile-Net v2 SSD-based deep learning model\cite{15} as a base and removed the last layer with a combined optic disc and tumor detection. To train this model, we manually labelled optic disc and tumors in fundus images with rectangular boxes. A total of 327 images were labelled where 285 images were used for training and 42 images were used for validation. The modified deep learning network was trained on the labelled optic disc and tumor fundus images.

After the optic disc and tumors were identified with a degree of confidence, the relative distance between them and the size of the tumor were estimated.
Estimation of tumor size was performed with a reference diameter of 1.5mm for optic disc (Figure 2C) when the latter was detected in an image. In the absence of an optic disc within the image frame, the calculation was based on the hough circular diameter of 12 mm which was averaged from all images containing optic disc (Figure 2D).

Detection of tumor seeds was complex and the tumor seeds were identified by a two-step approach. The region of interest was identified by an OpenCV algorithm which was further processed by DL model to identify the seeds (Figure 2E and 2F). Identification of regions of interest was done in eight directions from the center of the tumor to the edge of the hough circle diameter of the image by calculating the mean of the pixel intensity. A threshold was determined using the minimum of these means. Once a threshold was established, another pass through the eight directions was performed to determine the areas of interest where there could be tumor seeds that have pixel intensity above the threshold and away from the tumor. Depending on the direction, a directional straight line or a diagonal, either a rectangle or a square area of interest was selected. A trained deep learning object classifier that is trained specifically for seeds detection was used to identify the presence of tumor seeds and when present, the maximum distance of the seeds from the nearest tumor was computed. This model was trained and validated on 132 images.

Localization of intraocular hemorrhage (Figure 2G and 2H) and blood vessels (Figure 2I and 2J) were mapped by OpenCV and combination of OpenCV & DL models respectively. Calculations of distance of tumor from optic disc and size of the tumor were based on OpenCV algorithms and
geometry respectively.

**Assigning group labels with RB classifier:**

Each of the fundus image was run through all the algorithms to obtain a feature vector that consisted of features including detection of optic disc, tumor detection, determination of tumor size ($\leq 3$ mm or $> 3$ mm), total number of tumors, detection of intraocular haemorrhage, localization of overlying retinal blood vessels, distance between optic disc and tumor, presence of subretinal/vitreous seeds, number of tumor seeds, and maximum distance between seeds and the nearest tumor ($\leq 3$ mm or $> 3$ mm). Using the group classification labels by experts, a decision tree machine learning model\textsuperscript{[17]} was trained. This RB classifier model was trained on 616 images and tested on 155 images.

The final RB classification was based on an ensemble of the RB classifier results of all the images of a given eye of the patient. Following analysis of all images of one eye, the highest label was assigned as the group label for the eye.

**Performance Metrics:**

Performance metrics were calculated for the entire data set which included both ‘training’ and ‘test’ images. Parameters assessed included overall accuracy, misclassification as RB, under-classification rates and over-classification rates. Sensitivity, specificity, positive predictive value, negative predictive value for detection of RB and classification of RB were calculated. Performance metrics were calculated for every image and also for every eye since each eye had multiple images ranging between 4 to 20.
Results

Seven hundred and seventy-one fundus photographs from 109 eyes of 62 patients diagnosed with treatment naïve unilateral or bilateral retinoblastoma between January 2017 and June 2021 were retrieved from the institutional database. Of 771 fundus images, 181 images had no tumor and 590 images had iRB based on review by 2 ocular oncologists. The eyes were normal (n=31) or harbored group A (n=1), B (n=22), C (n=8), D (n=23), and E (n=24) RB. Inter-observer variability in detection of RB or classification of RB was 0.98% for individual images and 0% based on cumulative results for each eye (Table 1).

Performance Metrics:

Labels predicted by the RB classifier against true labels assigned by the observers are depicted in Figure 3. Of 590 images with RB, the accuracy for detection of RB was 85%, with RB being detected in 500 images. While 90 images (15%) were misclassified as normal, RB was detected but under-classified in 45 images (8%). Thus, a total of 135 images (23%) were under-classified. Of 181 images with no tumor, RB was detected in 2 (1%). Metrics for grouping of eyes yielded higher accuracy: Of 78 eyes with RB, RB was identified in 75 (96%) with under-classification in 1 (1%) eyes, and misclassified as normal in 3 (4%). Thus a total of 4 eyes (5%) were under-classified. Of 31 normal eyes, 29 (94%) were classified as normal and 2 (6%) were misclassified as RB.
Test characteristics:

The sensitivity and specificity of the trained AI model for detection of RB in an image was 85% and 99% respectively. Of 109 eyes, the sensitivity and specificity for detection of RB by AI model was 96% and 94% respectively. The sensitivity and specificity of RB classification was 100% and 100% for group A, 82% and 98% for group B, 63% and 99% for group C; 78% and 98% for group D, and 92% and 91% for group E respectively. Test characteristics for eyes in each group are summarized in Table 2.

Discussion:

While there has been an increasing use of AI in daily life with Apple Inc.’s Siri and Amazon’s Alexa, there has also been increasing applications of AI and ML in healthcare. Despite increasing discussions about AI and ML in healthcare in the literature, it was estimated that 100% of US healthcare was delivered without any use of AI in 2017. However, it is predicted that there will be an increased use of AI and ML in healthcare in the future, with certain tasks being overpowered by AI-enabled technology.

In the field of ophthalmology, AI and ML has been capable of analysing quantifiable data and images, thus aiding in diagnosis and staging of various ocular pathologies including strabismus, refractive error, keratitis, keratoconus, cataracts, glaucoma, papilledema, optic disc abnormalities, diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity, thyroid eye disease, choroidal nevus and transformation to melanoma. AI has also been used in development of treatment algorithms, assessing treatment need, and prognostication of ocular
pathologies.[19-21]

Retinoblastoma is the most common malignant intraocular tumor in children with most patients presenting with advanced disease at presentation in lower and lower middle-income countries.[24-26] Advanced disease at presentation results in poor chances of vision, globe and life salvage. Locally advanced disease is mainly related to delayed presentation and delayed diagnosis.[24] The diagnosis of RB is mainly dependent on symptoms like leukocoria and strabismus and red reflex testing, while most countries do not have routine fundus screening protocols in children.[27] In this study, there were more number of group D and E (n=47; 60%) eyes during the study period compared to Groups A to C (n=31; 40%) eyes suggestive of higher proportion of patients with advanced RB at presentation.

Fundus photographs have been the basis for development of AI models for various retinal pathologies including diabetic retinopathy, age-related macular degeneration and retinopathy of prematurity. AI and ML for diabetic retinopathy screening using fundus photographs has shown a sensitivity of 88% to 100% and specificity of 91% to 99% in detecting moderate diabetic retinopathy or worse.[28-30] Fundus image analysis has assisted in AI-related screening for age-related macular degeneration with an accuracy of 88% to 92%.[31] Similarly, AI models have been developed for retinopathy of prematurity for detection of plus disease based on fundus photographs with 93% to 100% sensitivity and 78% to 94% specificity.[32,33]

In this study, we used fundus photographs of children with treatment naïve RB to develop an AI model for diagnosis and classification of RB. The most
common DL method used for analysis of medical images is convoluted neural network (CNN).[34] In our study, we developed multiple CNN based DL models and developed OpenCV based computer vision algorithms for extracting features and machine learning classification algorithm for RB classification based on the extracted features. With the use of DL and OpenCV algorithm, the AI model achieved a sensitivity of 96% and specificity of 94% for detection of RB.

ICIoR classification is based on quantifiable data such as size of tumor (< or > 3 mm), distance of tumor from optic disc and fovea, distance of tumor seeds from the tumor, and number of seeds. Using the DL models, this data could be extracted from the fundus images. This allowed classification of intraocular RB with the AI model which was based on fundus images and the quantitative data. The AI model achieved sensitivity of 63% to 100% and specificity of 91% to 100% for classification of RB based on ICIoR.

The limitations of the study include relatively smaller sample size and unequal distribution of RB in different groups based on ICIoR. Also, we have not tested this model on fundus images of different races or on fundus images captured on different cameras. Thus the applicability of this AI model in these above circumstances is unknown. However, this is the first AI model developed for detection and grouping of RB and there is scope for improving the accuracy of the model with use of more DL algorithms.

In conclusion, this AI tool is a promising screening tool for RB. It has shown high sensitivity and specificity for detection of RB, though the sensitivity and specificity is variable for grouping of intraocular RB. Based on our study, this
AI model performs well on images captured on wide-field fundus camera. If this AI model can be used on fundus images captured on an inexpensive non-mydriatic fundus camera, it can facilitate mass screening of children in the community, so as to diagnose RB early before the onset of leukocoria or strabismus.

**References:**


31. Burlina PM, Joshi N, Pekala M, Pacheco KD, Freund DE, Bressler NM.


Table 1: Group labels assigned to of 771 images from 109 eyes by observers*

<table>
<thead>
<tr>
<th>ICIoR Group</th>
<th>Images</th>
<th>Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>181</td>
<td>31</td>
</tr>
<tr>
<td>A</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>204</td>
<td>22</td>
</tr>
<tr>
<td>C</td>
<td>70</td>
<td>8</td>
</tr>
<tr>
<td>D</td>
<td>182</td>
<td>23</td>
</tr>
<tr>
<td>E</td>
<td>128</td>
<td>24</td>
</tr>
<tr>
<td>Total</td>
<td>771</td>
<td>109</td>
</tr>
</tbody>
</table>

*Interobserver variability between the two observers was 0.98% for images and 0% for eyes; ICIoR: International Classification for Intraocular Retinoblastoma

Table 2: Performance metrics of RB classifier

<table>
<thead>
<tr>
<th>Detection</th>
<th>Normal</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>For individual images</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>85%</td>
<td>99%</td>
<td>17%</td>
<td>79%</td>
<td>84%</td>
<td>73%</td>
</tr>
<tr>
<td>Specificity</td>
<td>99%</td>
<td>85%</td>
<td>100%</td>
<td>96%</td>
<td>97%</td>
<td>97%</td>
</tr>
<tr>
<td>PPV</td>
<td>100%</td>
<td>67%</td>
<td>100%</td>
<td>87%</td>
<td>73%</td>
<td>89%</td>
</tr>
<tr>
<td>NPV</td>
<td>67%</td>
<td>100%</td>
<td>95%</td>
<td>93%</td>
<td>98%</td>
<td>92%</td>
</tr>
<tr>
<td>For all images of an eye</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>96%</td>
<td>94%</td>
<td>100%</td>
<td>82%</td>
<td>63%</td>
<td>78%</td>
</tr>
<tr>
<td>Specificity</td>
<td>94%</td>
<td>96%</td>
<td>100%</td>
<td>98%</td>
<td>99%</td>
<td>98%</td>
</tr>
<tr>
<td>PPV</td>
<td>97%</td>
<td>91%</td>
<td>100%</td>
<td>90%</td>
<td>83%</td>
<td>90%</td>
</tr>
<tr>
<td>NPV</td>
<td>91%</td>
<td>98%</td>
<td>100%</td>
<td>96%</td>
<td>97%</td>
<td>94%</td>
</tr>
<tr>
<td>---------</td>
<td>-----</td>
<td>-----</td>
<td>------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
</tbody>
</table>

RB: retinoblastoma; PPV: positive predictive value; NPV: negative predictive value

Figure 1: Overview of methodology employed in training and testing of retinoblastoma classifier

![Feature Extraction & Technology Diagram]

Figure 2: Algorithms used for identification features from fundus images

(A) & (B): Bounding boxes with confidence score for optic disc and tumor

(C) & (D): Calculation of tumor size with with reference to optic disc and hough circle respectively

(E) & (F): Identification of regions of interest (tumor seeds) and vitreous seeds within mapped areas of interest by OpenCV algorithm and Deep Learning model
(G) & (H): Mapping of hemorrhage overlying the tumor using by combination of OpenCV and Deep Learning methods

(I) to (J): Mapping of blood vessels overlying the tumor by combination of OpenCV and Deep Learning methods

Figure 3: Performance metrics of retinoblastoma (RB) classifier for detection and classification of retinoblastoma

(A) & (B): Grids depicting labels assigned by observers versus labels assigned by RB classifier for 771 images and 109 eyes respectively
(C) & (D): Graphical summary of accurate, over-classification and under-classification by RB classifier in 771 images and 109 eyes respectively.
LEARNING CURVE IN THE CONSTRUCT OF SMARTPHONE-BASED KERATOSCOPE PROTOTYPE FOR KCN SCREENING

Corneal tomography in fellow eyes of unilateral keratoconus for detection of subclinical keratoconus

Abstract

Purpose:

To analyze topographic and tomographic changes in fellow eyes of unilateral keratoconus patients by comparing them with normal eyes.

Methods:

This five year retrospective observational comparative case study included 15 advanced keratoconus eyes of unilateral keratoconus (KCN group), 15 normal fellow eyes of unilateral keratoconus (Fellow eye group) and 34 eyes of normal refractive surgery candidates (Normal group). Topographic and tomographic data, data from enhanced elevation maps, and keratoconus
indices were measured in all study eyes using Pentacam. Receiver operating characteristic (ROC) curves were used to evaluate the area under the curve (AUC), sensitivity and specificity of each parameter and identify cut-off points in discriminating between the fellow and normal eyes.

**Results:**

Corneal thickness at the apex (CTA, $P = 0.001$) and at the thinnest point (CTT, $P < 0.001$), corneal volume (CV, $P = 0.007$), Belin/Ambrosio Enhanced Ectasia Display (BAD) - thinnest point (Dt, $P = 0.002$) and thinnest point displacement (Da, $P = 0.002$) were significantly lower in the fellow group compared to eyes of normal subjects. On ROC curve analysis, the most efficient distinguishing indices between the fellow group and normal controls were BAD - overall D value (AUC = 0.859), Dt (AUC =0.827), Da (AUC = 0.789) followed by pachymetric progression index maximum (AUC = 0.741).

**Conclusion:**

BAD-D value and pachymetric progression index could be useful in detecting the earliest form of subclinical keratoconus. However, every single parameter alone is not enough to detect early changes; a combination of different data is required to distinguish subclinical keratoconus.

**Keywords:**

Belin/Ambrosio enhanced ectasia display, Pentacam, tomography, topography, unilateral keratoconus
**Introduction**

Detecting keratoconus in its earliest stage is one of the most important aspects of avoiding iatrogenic corneal ectasia after refractive surgery. Based on a large series of cases reported in the literature, Randleman et al. proposed a score that can be used to predict the risk of ectasia (Ectasia Risk Score) to prevent the development of post-refractive surgery corneal ectasia. This score takes into account the preoperative topographic appearance, the preoperative central corneal thickness, the residual posterior wall, the patient’s age, and the planned correction.[1] Among these various parameters, the presence of undiagnosed early keratoconus is the leading risk factor for post-refractive surgery ectasia.[2] Studies suggest that subclinical or clinical keratoconus is found in 1-6% of myopic patients undergoing refractive surgery.[3-5] Advanced keratoconus can be diagnosed with typical biomicroscopic, retinoscopic and topographic findings. However, detection of the disease in the preclinical stage is difficult.

In literature, there were multiple terms referring to the earliest stage of keratoconus, which were frequently misused and caused confusion, including subclinical keratoconus, keratoconus suspect (KCS) and forme fruste keratoconus (FFKC).[6-9] The term KCS was reserved for the cornea with some anterior topographic changes of keratoconus but without evidence of clinical keratoconus in either eye. The term FFKC was first described by Amsler as an incomplete, abortive or unusual form of a syndrome of disease, meaning corneas that have subtle topographic characteristics but do not reach the threshold of keratoconus suspect.[7]
However, due to the ambiguity of definition and significant overlap between these terms, there are no definitive criteria to distinguish subclinical keratoconus from normal.

Pentacam is considered to be the most sensitive device for detecting the early form of keratoconus using various parameters such as corneal thickness spatial profile, the percentage of thickness increase, and Belin/Ambrosio Enhanced Ectasia Display (BAD).\textsuperscript{[10-14]} The purpose of this study was to evaluate the characteristics of the subtle changes in subclinical keratoconus and compare it with normal eyes. Previous research shows that true unilateral keratoconus is rare and that the normal fellow eye is believed to have subclinical keratoconus.\textsuperscript{[14]} Hence, the normal fellow eye in unilateral keratoconus may be the ideal model for the earliest form of subclinical keratoconus. In the present study, normal fellow eyes in unilateral keratoconus patients were considered as the mildest form of subclinical keratoconus, and topographic and tomographic parameters were compared with normal eyes using Pentacam.

**Methods**

This 5-year retrospective observational comparative case study included patients with unilateral keratoconus diagnosed by Pentacam and candidates for refractive surgery with normal corneas. Clinical records of 49 patients (64 eyes) were retrospectively analyzed. The ethical committee approval was obtained, and the tenets of the Declaration of Helsinki were followed for all study procedures. The study was registered in Clinical Trials Registry - India (CTRI).
The study subjects were divided into 3 groups: 15 advanced keratoconus eyes of unilateral keratoconus patients (KCN group), 15 normal fellow eyes of unilateral keratoconus patients (Fellow eye group) and 34 eyes of normal refractive surgery candidates (Normal group). Eyes were diagnosed as keratoconus based on Pentacam rotating Scheimpflug camera–derived topographic/tomographic parameters and criteria used in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study.\cite{15} Patients with advanced keratoconus in 1 eye and a normal fellow eye were defined as unilateral keratoconus. In this study, fellow eyes in unilateral keratoconus should not only be clinically normal but also satisfy all of the following criteria determined by the Pentacam: normal index of topographic and tomographic keratoconus classification with final D value $< 1.6$ standard deviation (SD) from the BAD. Normal control patients were myopic or myopic astigmatism candidates for refractive surgery with clinically normal corneas and topographic/tomographic characteristics within normal limits determined by the Pentacam. All normal control patients underwent uncomplicated refractive surgery, either Small incision lenticule extraction (SMILE) or Femto-laser-assisted in situ keratomileusis (LASIK) and had a 6-month follow-up without any evidence of ectatic corneal changes. In the normal group, only left eyes were used in the study analysis.

Exclusion criteria included a history of ocular surgery, history of ocular trauma, any other ocular pathology and significant corneal scarring that might potentially affect the outcomes. All patients were asked to stop wearing soft contact lenses for at least 1 week and rigid gas-permeable contact lenses for at least 3 weeks before the examination. A complete ocular
examination including slit lamp biomicroscopy, cycloplegic refraction, best corrected distance visual acuity (BCVA) using Snellen acuity chart, keratometry readings, intraocular pressure measurement and dilated fundus examination was performed.

Topographic and tomographic examinations were performed using the Pentacam rotating Scheimpflug camera (Oculus, Wetzlar, Germany). Image quality was checked, and for each eye, only one examination with a good quality factor was recorded. Various parameters were derived from topographic and topometric maps and the BAD, as described below.

Data from topographic maps: flat keratometry (K1), steep keratometry (K2), mean keratometry (Km) for the central 3.0 mm of the cornea, maximum keratometry (Kmax), topographic astigmatism (A), asphericity for the anterior corneal surfaces (Q), keratometric asymmetry: inferior-superior asymmetry at 4 and 6 mm (4 mm I-S and 6 mm I-S), superotemporal-inferonasal asymmetry at 4 and 6 mm (4 mm ST-IN and 6 mm ST-IN), and superonasal-inferotemporal asymmetry at 4 and 6 mm (4 mm SN-IT and 6 mm SN-IT) radius ring of the cornea, corneal volume (CV) in 7 mm diameter centered on the anterior corneal apex, corneal thickness at the apex (CTA) and at the thinnest point of the cornea (CTT) with y coordinate of the thinnest local (Y).

Data from elevation maps: maximum elevations on anterior (AEmax) and posterior cornea (PEmax), minimum elevations on anterior (AEmin) and posterior cornea (PEmin), elevation differences (maximum-minimum) on anterior (AEdif) and posterior cornea (PEdif) in the central 3 mm zone.
Data from topometric maps: index of surface variance (ISV), index of vertical asymmetry (IVA), keratoconus-index (KI), center keratoconus-index (CKI), index of height asymmetry (IHA), index of height decenteration (IHD), and radii minimum (Rmin).

Data from the BAD: D values representing the front surface (Df), back surface (Db), pachymetric progression (Dp), thinnest point (Dt), thinnest point displacement (Da), and final (D), pachymetric progression indices – maximum (PImax), minimum (PImin) and average (PIavg).

**Statistical analysis**

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD. The normality of data was tested by the Kolmogorov Smirnov test. Qualitative variables were compared using Pearson's Chi-Square test/Fisher's exact test. One way ANOVA was used to test the mean values between the 3 groups, followed by Tukey HSD Post-hoc test for multiple comparisons. The receiver operating characteristic (ROC) curve with area under the curve (AUC) was plotted for Pentacam parameters between the 3 groups. The diagnostic specificity and sensitivity of the main parameters (AUC >0.7) for distinguishing fellow eyes from normal eyes were evaluated, and cut-off points were presented. A probability value (P value) less than 0.05 was considered as significant at 95% confidence level. The statistical package for social sciences (SPSS) version 24.0 was used in the analysis.

**Results**

Fifteen eyes of 15 unilateral keratoconus patients (10 males and 5 females)
and 34 eyes of 34 normal refractive surgery candidates were analyzed (17 males and 17 females). Out of 15 unilateral keratoconus eyes, advanced keratoconus manifested in 11 left eyes and 4 right eyes, which was statistically significant (P < 0.001). The ratio of male to female patients was 2:1 in the unilateral KCN group and 1:1 in the Normal group, respectively. The mean age was 26.4 ± 4.08 (range: 18-33) years in the unilateral KCN and 25.22 ± 4.24 (range: 18-35) years in the normal, which was not statistically different.

KCN vs. Fellow eye group: There were significant differences (P ≤ 0.001) between the KCN and fellow eye group in almost all measured parameters except for corneal volume (CV), superotemporal-inferonasal asymmetry at 4 mm (4 mm ST-IN) and y coordinate of the thinnest local point (Y) [Table 1] and [Table 2].

KCN vs. Normal group: There were significant differences (P ≤ 0.001) between the KCN and normal eye group in all measured parameters [Table 1] and [Table 2].

Fellow eye vs Normal group: There were significant differences between the fellow eye and normal group in 5 parameters: corneal thickness at the apex (CTA, P = 0.001) and at the thinnest point of the cornea (CTT, P < 0.001), corneal volume (CV, P = 0.007), BAD - thinnest point (Dt, P = 0.002) and thinnest point displacement (Da, P = 0.002) [Table 1] and [Table 2].

Receiver operating characteristic (ROC) curve analysis

When discriminating Fellow eye group from Normal group, the D value showed the highest AUC (0.859), followed by Dt (0.827) and Da (0.789)
[Table 3]. In discriminating between KCN group and Normal group, most parameters had high AUCs [Table 3].

[Table 4] shows the cut-off points and sensitivity and specificity values of the main Pentacam parameters derived from ROC curve analysis used to discriminate between Fellow eye in unilateral keratoconus and Normal groups. [Figure 1] presents the graphical representation of the ROC curve of Pentacam parameters between Fellow eye and Normal groups.

Discussion

Many studies investigated early screening and diagnosis of keratoconus using the Pentacam device in different ethnic populations.[9-11,16-26] Results varied in different populations related to race, geographic location, and size of the study population. Most such studies differed from each other by the criteria used to diagnose subclinical/FFKC.[11,16-20,25,26] To the best of our knowledge, the present study is the first and only study to identify characteristics of the subtle morphologic changes in the fellow eyes of unilateral keratoconus patients in Indian population.

In the present study, fellow eyes of unilateral keratoconus patients showed normal values with respect to not only topographic but also tomographic parameters in Pentacam. This may be explained by the fact that fellow eye in our study was defined as the earliest form, with normal elevation and pachymetric values, including the final D value in BAD.

The preponderance towards males in the population in this study is consistent with other keratoconus incidence studies.[21,24] CTA, CTT, CV, BAD-Dt, and Da were significantly different in the fellow group and normal
group; these results are very comparable to those of other studies,[9,11,16,17,19,20,25] However, the fellow eye in the present study was defined as normal, not only in the anterior curvature, but also in the elevation, pachymetric, and BAD maps.

In this study, D value was the most characteristic index between the fellow and normal groups and showed the highest area under the ROC curve. The cut-off for D value to differentiate fellow eyes from normal eyes was found to be 0.835, with 93.3% sensitivity but limited specificity. On the other hand, the cut-off for D value in differentiating keratoconus from normal eyes was found to be 1.965, with a sensitivity of 100%. The D value is a multimetric combination parameter composed of keratometric, pachymetric, pachymetric progression, and posterior elevation parameters. Similar to this study, D value had the highest area under the ROC curve to differentiate between subclinical keratoconus eyes and control eyes in the studies done by Muftuoglu et al., Ruisenor Vazquez et al., and Huseynli et al.[17,19,25] This result suggests that the D index can be useful as a sole parameter in diagnosing early subclinical keratoconus.

Pachymetric progression index maximum (PImax) was also considered as a valuable parameter in discriminating fellow eyes with normal eyes in this study, consistent with the reports by Uçakhan et al., Ruisenor Vazquez et al., and Huseynli et al.[16,19,25] The cut-off for PImax to differentiate fellow eyes from normal eyes was found to be 1.155, with 93.3% sensitivity but limited specificity.

Pinero et al. reported progressively lower pachymetric readings in eyes with
subclinical, early, or moderate keratoconus (P < 0.01) and significantly lower CV in the moderate keratoconus group than in the subclinical and mild groups (P = 0.04). A possible explanation for this finding may be that at the early stages of keratoconus, a redistribution of CV occurs with no loss of tissue.\textsuperscript{[11]} As discussed, we found significant differences in CCT, CTA, and CV between normal eyes and fellow eyes of unilateral keratoconus.

Uçakhan et al. evaluated Pentacam parameters in mild to moderate keratoconus, subclinical keratoconus, and normal eyes with myopic astigmatism. They defined subclinical keratoconus as the fellow eye of keratoconus with abnormal topographic features (inferior-superior asymmetry or bow-tie pattern with skewed radial axis) and found that corneal thickness distribution indices and posterior elevation data were more helpful than anterior elevation data in identifying eyes with subclinical keratoconus.\textsuperscript{[16]} This is similar to the observations of the present study. Bae et al., on the other hand, found that keratometric asymmetry, topometric index and anterior/posterior elevation difference had a higher discriminative ability than pachymetric parameters in detecting the earliest form of subclinical keratoconus.\textsuperscript{[18]}

Huseynli et al. evaluated scheimpflug tomography parameters in subclinical keratoconus, clinical keratoconus, and normal Caucasian eyes. They defined subclinical keratoconus as clinically normal eyes with abnormal topographic features and observed that D value, elevation parameters, and pachymetric progression indices could effectively differentiate subclinical keratoconus from normal corneas in a Caucasian population.\textsuperscript{[25]} This is in comparison with the results of the present study.
As discussed above, our study is the first and only study to identify early topometric and tomographic changes in the fellow eyes of unilateral keratoconus patients in the Indian population, and we had included only those fellow eyes which were normal in the anterior curvature, elevation, pachymetric, and the BAD maps.

The limitation of this study was its relatively small sample size. The incidence of true unilateral keratoconus is rare, and thus, this is unlikely to skew the results of this study. Further studies with larger sample size and simultaneous evaluation of the corneal biomechanics and wave front aberrations may be more useful for early detection of subclinical keratoconus.

**Conclusion**

Our study showed that the BAD-D value and pachymetric progression index were more effective than other Pentacam parameters in detecting the earliest form of subclinical keratoconus. The present study supports findings previously reported on the usefulness of Scheimpflug imaging to assess subclinical keratoconus in different populations and confirms results indicating that any single parameter alone is not enough to detect early changes. A combination of different data is required to distinguish subclinical keratoconus.

**References**


Figure legends

Figure 1: Receiver operating characteristic (ROC) curve of Pentacam parameters between Fellow eye and Normal groups
Table 1: Mean pentaacam parameters in KCN, fellow eye, and normal groups

<table>
<thead>
<tr>
<th>Pentacam parameters</th>
<th>KCN group (n=56), mean (SD)</th>
<th>Fellow eye group (n=56), mean (SD)</th>
<th>Normal group (n=34), mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K1</td>
<td>4.18 (4.11)</td>
<td>4.71 (0.99)</td>
<td>4.95 (1.37)</td>
</tr>
<tr>
<td>K2</td>
<td>4.90 (5.14)</td>
<td>4.69 (1.11)</td>
<td>4.03 (1.49)</td>
</tr>
<tr>
<td>Km</td>
<td>4.74 (4.22)</td>
<td>4.21 (1.92)</td>
<td>4.47 (1.4)</td>
</tr>
<tr>
<td>Kmax</td>
<td>5.48 (4.1)</td>
<td>4.39 (1.15)</td>
<td>4.57 (1.47)</td>
</tr>
<tr>
<td>A</td>
<td>4.09 (4.0)</td>
<td>0.96 (0.41)</td>
<td>1.98 (0.44)</td>
</tr>
<tr>
<td>Q</td>
<td>-0.78 (0.64)</td>
<td>-0.03 (0.14)</td>
<td>-0.26 (0.09)</td>
</tr>
<tr>
<td>4 mm I-S</td>
<td>12.64 (6.51)</td>
<td>0.27 (0.94)</td>
<td>0.06 (0.46)</td>
</tr>
<tr>
<td>6 mm I-S</td>
<td>5.45 (4.83)</td>
<td>0.58 (1.07)</td>
<td>0.03 (1.0)</td>
</tr>
<tr>
<td>4 mm ST-I</td>
<td>-3.07 (5.22)</td>
<td>-0.04 (0.64)</td>
<td>-0.38 (2.54)</td>
</tr>
<tr>
<td>6 mm ST-I</td>
<td>-2.69 (4.39)</td>
<td>0.28 (0.59)</td>
<td>0.1 (0.2)</td>
</tr>
<tr>
<td>4 mm SN-I</td>
<td>-9.12 (6.7)</td>
<td>0.35 (1.7)</td>
<td>0.06 (1.0)</td>
</tr>
<tr>
<td>6 mm SN-I</td>
<td>-5.41 (5.1)</td>
<td>-0.21 (2.64)</td>
<td>-0.41 (0.65)</td>
</tr>
<tr>
<td>CV</td>
<td>56.89 (2.7)</td>
<td>56.3 (3.13)</td>
<td>61.01 (2.62)</td>
</tr>
<tr>
<td>CTA</td>
<td>407.8 (23.4)</td>
<td>315.07 (20.04)</td>
<td>540.24 (23.39)</td>
</tr>
<tr>
<td>CTT</td>
<td>455.13 (29.23)</td>
<td>512.2 (26.79)</td>
<td>544.12 (23.46)</td>
</tr>
<tr>
<td>Y</td>
<td>-0.64 (0.47)</td>
<td>-0.45 (0.18)</td>
<td>-0.3 (0.19)</td>
</tr>
<tr>
<td>Aeffeas</td>
<td>99.47 (16.6)</td>
<td>3.13 (0.32)</td>
<td>2.92 (0.13)</td>
</tr>
<tr>
<td>Bfmax</td>
<td>57.27 (24.1)</td>
<td>5.27 (1.94)</td>
<td>4.12 (2.98)</td>
</tr>
<tr>
<td>Aemiin</td>
<td>-10.93 (7.91)</td>
<td>-0.47 (1.68)</td>
<td>-1.26 (0.99)</td>
</tr>
<tr>
<td>PEmiin</td>
<td>-17.87 (14.93)</td>
<td>-1.67 (2.69)</td>
<td>-2.18 (3.5)</td>
</tr>
<tr>
<td>ASIA</td>
<td>4.06 (20.24)</td>
<td>3.6 (1.55)</td>
<td>3.99 (1.16)</td>
</tr>
<tr>
<td>CGL</td>
<td>75.1 (32.7)</td>
<td>69.3 (3.22)</td>
<td>62.92 (3.98)</td>
</tr>
<tr>
<td>ISV</td>
<td>102.8 (47.8)</td>
<td>16.13 (2.47)</td>
<td>13.52 (4.27)</td>
</tr>
<tr>
<td>IVA</td>
<td>1.18 (0.29)</td>
<td>0.11 (0.24)</td>
<td>0.11 (0.44)</td>
</tr>
<tr>
<td>KE</td>
<td>1.29 (0.18)</td>
<td>1.02 (0.32)</td>
<td>1.02 (0.62)</td>
</tr>
<tr>
<td>CHG</td>
<td>1.04 (0.07)</td>
<td>1.00 (0.01)</td>
<td>(0.31)</td>
</tr>
<tr>
<td>SIA</td>
<td>32.3 (34.55)</td>
<td>5.43 (5.43)</td>
<td>5.9 (3.93)</td>
</tr>
<tr>
<td>IHD</td>
<td>5.15 (2.5)</td>
<td>0.81 (0.31)</td>
<td>0.01 (0)</td>
</tr>
<tr>
<td>Rmiic</td>
<td>5.06 (0.6)</td>
<td>7.56 (0.18)</td>
<td>7.56 (0.26)</td>
</tr>
<tr>
<td>PI max</td>
<td>3.94 (2.34)</td>
<td>1.11 (1.3)</td>
<td>1.17 (1.06)</td>
</tr>
<tr>
<td>Fmiic</td>
<td>1.35 (0.68)</td>
<td>0.73 (0.11)</td>
<td>0.65 (0.16)</td>
</tr>
<tr>
<td>Fexa</td>
<td>2.3 (1.1)</td>
<td>1.03 (0.13)</td>
<td>0.93 (0.12)</td>
</tr>
<tr>
<td>Gf</td>
<td>10.92 (7.14)</td>
<td>0.21 (0.32)</td>
<td>-0.08 (0.04)</td>
</tr>
<tr>
<td>Db</td>
<td>3.01 (0.76)</td>
<td>-0.04 (0.56)</td>
<td>-0.36 (0.62)</td>
</tr>
<tr>
<td>Dr</td>
<td>9.43 (7.5)</td>
<td>0.53 (0.37)</td>
<td>0.10 (0.43)</td>
</tr>
<tr>
<td>Ds</td>
<td>2.07 (1.13)</td>
<td>0.81 (0.35)</td>
<td>-0.15 (0.05)</td>
</tr>
<tr>
<td>Da</td>
<td>3.1 (3.56)</td>
<td>0.92 (0.52)</td>
<td>0.13 (0.44)</td>
</tr>
<tr>
<td>D</td>
<td>9.18 (4.05)</td>
<td>1.18 (0.32)</td>
<td>0.54 (0.54)</td>
</tr>
</tbody>
</table>

SD=Standard deviation, n=Number of eyes: KCN=Keratoconus. K1=Flat keratometry, K2=Steep keratometry, Km=Mean keratometry, Kmax=Maximum keratometry, A=Topographic astigmatism, Q=Asphericity for the anterior corneal surface: 4mm I-S=Keratometry inferior-superior asymmetry at 4 mm, 6 mm I-S=Keratometry inferior-superior asymmetry at
6mm. 4mm ST-IN=Superotemporal-interonasal asymmetry at 4 mm, 6mm ST-IN=Superotemporal-inferonasal asymmetry at 6 mm

4mm SN-IT=Superonasal-interotemporal asymmetry at 4mm, 6mm SN-IT=Superonasal-inferotemporal asymmetry at 6mm, CV=Corneal volume: CTA=Corneal thickness at the apex: CTT=Corneal thickness at the thinnest point, Y=Y coordinate of the thinnest local, AEmax=Maximum elevation on anterior comes, PE=Maximum elevation on posterior cornea, AEmin=Minimum elevation on anterior cornea, PEn=Minimum elevation on posterior cornea, AEdif=Elevation differences on anterior cornea, PE=Variance of surface variance, IVA=Index of vertical asymmetry, KI=Keratoconus-index, CKI=Centre keratoconus-index, IHA=Index of height asymmetry. IHD=Index of height decentration, Rmin=Radius minimum: Df=BeliniAmbrosio enhanced ectasia display value representing the front surface. Db: Back surface, Dp=Pachymetric progression, Dt=Thinnest point displacement, D=Overall deviation, Pl=Pachymetric progression index maximum, Pl=Pachymetric progression index minimum: Plavg=Pachymetric progression index average.

Table 2: Comparison of Pentacam parameters between KCN, Fellow eye and Normal groups

<table>
<thead>
<tr>
<th>Pentacam parameters</th>
<th>KCN vs Fellow eye</th>
<th>KCN vs</th>
<th>Fellow eye vs Normal P</th>
</tr>
</thead>
<tbody>
<tr>
<td>K1</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>0.949</td>
</tr>
<tr>
<td>K2</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.912</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>Km</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.934</td>
</tr>
<tr>
<td>Kmax</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.989</td>
</tr>
<tr>
<td>A</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.931</td>
</tr>
<tr>
<td>Q</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.009</td>
</tr>
<tr>
<td>4 mm I-S</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.97</td>
</tr>
<tr>
<td>6 rnm I-S</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.756</td>
</tr>
<tr>
<td>4 rnm ST-IN</td>
<td>0.15</td>
<td>0.001</td>
<td>0.999</td>
</tr>
<tr>
<td>6 rnm ST-IN</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>0.962</td>
</tr>
<tr>
<td>4 rnm SN-IT</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.988</td>
</tr>
<tr>
<td>6 mm SN-IT</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.947</td>
</tr>
<tr>
<td>CV</td>
<td>0.366</td>
<td>&lt;0.001</td>
<td>0.007</td>
</tr>
<tr>
<td>CTA</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>CTT</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Y</td>
<td>0.138</td>
<td>&lt;0.001</td>
<td>0.189</td>
</tr>
<tr>
<td>AErnanx</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.992</td>
</tr>
<tr>
<td>PERnanx</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.96</td>
</tr>
<tr>
<td>AErnin</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.985</td>
</tr>
<tr>
<td>PERnin</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.975</td>
</tr>
<tr>
<td>AEdif</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.984</td>
</tr>
<tr>
<td>PEdif</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.99</td>
</tr>
<tr>
<td>ISV</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.997</td>
</tr>
<tr>
<td>IVA</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.999</td>
</tr>
<tr>
<td>KI</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.98</td>
</tr>
<tr>
<td>CKI</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.997</td>
</tr>
<tr>
<td>IHA</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.958</td>
</tr>
<tr>
<td>IHD</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.995</td>
</tr>
<tr>
<td>Rmin</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>Plmax</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.918</td>
</tr>
<tr>
<td>Plmin</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.697</td>
</tr>
<tr>
<td>Plavg</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.828</td>
</tr>
<tr>
<td>Df</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.963</td>
</tr>
<tr>
<td>-----</td>
<td>--------</td>
<td>--------</td>
<td>-------</td>
</tr>
<tr>
<td>Db</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.93</td>
</tr>
<tr>
<td>Dp</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.826</td>
</tr>
<tr>
<td>Dt</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>Da</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>D</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.552</td>
</tr>
</tbody>
</table>

Table 3: Receiver operating characteristic curve (ROC) analysis for KCN and Fellow eye versus Normal groups

<table>
<thead>
<tr>
<th>Pentacam parameters</th>
<th>KCN vs Normal</th>
<th>Fellow eye vs Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUG (CI 95%)</td>
<td>AUC (CI 95%)</td>
</tr>
<tr>
<td>K1</td>
<td>0.74 (0.562-0.919)</td>
<td>0.431 (0.266-0.597)</td>
</tr>
<tr>
<td>K2</td>
<td>0.892 (0.77-1.014)</td>
<td>0.411 (0.244-0.577)</td>
</tr>
<tr>
<td>Km</td>
<td>0.833 (0.692-0.975)</td>
<td>0.427 (0.261-0.593)</td>
</tr>
<tr>
<td>Kmax</td>
<td>0.981 (0.946-1.016)</td>
<td>0.45 (0.281-0.619)</td>
</tr>
<tr>
<td>A</td>
<td>0.969 (0.928-1.01)</td>
<td>0.457 (0.274-0.639)</td>
</tr>
<tr>
<td>Q</td>
<td>0.148 (-0.13-0.309)</td>
<td>0.387 (0.204-0.571)</td>
</tr>
<tr>
<td>4 mm I-S</td>
<td>1 (1)</td>
<td>0.519 (0.334-0.703)</td>
</tr>
<tr>
<td>6mm I-S</td>
<td>0.989 (0.969-1.01)</td>
<td>0.629 (0.46-0.799)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>---------</td>
<td>------------------</td>
</tr>
<tr>
<td>4 mm ST-IN</td>
<td>0.206</td>
<td>0.512</td>
</tr>
<tr>
<td>6 mm ST-IN</td>
<td>0.195</td>
<td>0.598</td>
</tr>
<tr>
<td>4 mm SN-IT</td>
<td>0.005</td>
<td>0.457</td>
</tr>
<tr>
<td>6 mm SN-IT</td>
<td>0.025</td>
<td>0.377</td>
</tr>
<tr>
<td>CV</td>
<td>0.138</td>
<td>0.249</td>
</tr>
<tr>
<td>CTA</td>
<td>0.008</td>
<td>0.187</td>
</tr>
<tr>
<td>CTT</td>
<td>0</td>
<td>0.171</td>
</tr>
<tr>
<td>Y</td>
<td>0.233</td>
<td>0.28</td>
</tr>
<tr>
<td>AErnax</td>
<td>1</td>
<td>0.605</td>
</tr>
<tr>
<td>PErnax</td>
<td>1</td>
<td>0.636</td>
</tr>
<tr>
<td>AErnin</td>
<td>0.005</td>
<td>0.485</td>
</tr>
<tr>
<td>PErnin</td>
<td>0.122</td>
<td>0.544</td>
</tr>
<tr>
<td>AEdif</td>
<td>1</td>
<td>0.584</td>
</tr>
<tr>
<td>PEdif</td>
<td>1</td>
<td>0.564</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>ISV</td>
<td>0.998 (0.992-1.004)</td>
<td>0.605 (0.435-0.775)</td>
</tr>
<tr>
<td>IVA</td>
<td>1 (1)</td>
<td>0.508 (0.322-0.694)</td>
</tr>
<tr>
<td>KI</td>
<td>1 (1)</td>
<td>0.589 (0.418-0.76)</td>
</tr>
<tr>
<td>CKI</td>
<td>0.846 (0.682-1.01)</td>
<td>0.533 (0.342-0.724)</td>
</tr>
<tr>
<td>IHA</td>
<td>0.846 (0.689-1.004)</td>
<td>0.327 (0.131-0.524)</td>
</tr>
<tr>
<td>IHD</td>
<td>0.989 (0.966-1.013)</td>
<td>0.336 (0.133-0.54)</td>
</tr>
<tr>
<td>Rmin</td>
<td>0.017 (-0.15-0.048)</td>
<td>0.53 (0.363-0.698)</td>
</tr>
<tr>
<td>Plmax</td>
<td>0.997 (0.989-1.005)</td>
<td>0.741 (0.602-0.88)</td>
</tr>
<tr>
<td>Plmin</td>
<td>0.947 (0.882-1.012)</td>
<td>0.689 (0.532-0.846)</td>
</tr>
<tr>
<td>Plavg</td>
<td>0.998 (0.992-1.004)</td>
<td>0.693 (0.536-0.851)</td>
</tr>
<tr>
<td>Df</td>
<td>0.986 (0.957-1.015)</td>
<td>0.598 (0.432-0.764)</td>
</tr>
<tr>
<td>Db</td>
<td>0.988 (0.963-1.013)</td>
<td>0.648 (0.495-0.801)</td>
</tr>
<tr>
<td>Dp</td>
<td>0.998 (0.992-1.004)</td>
<td>0.695 (0.538-0.852)</td>
</tr>
<tr>
<td>Dt</td>
<td>1 (1)</td>
<td>0.827 (0.693-0.962)</td>
</tr>
<tr>
<td></td>
<td>Da</td>
<td>0.998 (0.992-1.004)</td>
</tr>
<tr>
<td>-------</td>
<td>----------</td>
<td>---------------------</td>
</tr>
<tr>
<td>D</td>
<td>1 (1)</td>
<td>0.859 (0.756-0.961)</td>
</tr>
</tbody>
</table>

AUC = Area under the receiver operating characteristic curve; CI = Confidence interval
EFFICACY OF INTRALESIONAL BLEOMYCIN IN TREATMENT OF ORBITAL LYMPHANGIOMAS

ABSTRACT:

Objective:

To study the effectiveness of intralesional bleomycin injection in orbital lymphangiomas. Methods: 16 patients diagnosed with orbital lymphangiomas were included in this prospective study. All of them received intralesional bleomycin injection at a dose of 0.5mg/kg body weight (maximum 15mg) along with 2% lignocaine. Patients who required repeat injections were based on the documentation of serial clinical and radiological response to treatment. Repeat injections were given once in every 4 weeks. Results: Proptosis and lid swelling was the common presenting sign. All patients were treated with 2-4 injections of bleomycin. The follow up period ranged from 6-18 months. 11 patients had complete resolution, 3 patients had poor response and required surgical excision and
remaining 2 patients had recurrence. Conclusion: Intralesional bleomycin therapy is an effective and safe method of treatment of orbital lymphangioma without any significant ophthalmic or systemic side effects.

KEYWORDS: ORBITAL LYMPHANGIOMA, BLEOMYCIN, PROPTOSIS

INTRODUCTION:

Lymphangiomas are benign lymphatic tumors, characterized by proliferation of anomalous dilated lymphatic vessels lined by normal endothelial cells. Initially considered as a neoplasm, now the International Society for the Study of Vascular Anomalies (ISSVA) has classified lymphangiomas as combined vascular malformations within the spectrum of arterial, venous and lymphatic lesions that have characteristics of venous and lymphatic components. Orbital lymphangioma represents 0.3%–4% of all orbital tumors. Depending on the location they can be classified as deep or superficial lymphangiomas. They can remain silent clinically or enlarge slowly causing proptosis, extraocular motility restriction and sudden engorgement due to intralesional haemorrhage causing compressive optic neuropathy. Ideally surgical excision is the main stay of treatment but due the extensive infiltrative nature of the lesion, complete surgical excision is dangerous due to risk of damage to adjacent vital structures. Hence recurrence is very common in case of incomplete removal of the lesion. Therefore, non-surgical methods such as intralesional sclerosing agents have been tried. In our study we have assessed the role and efficacy of intralesional bleomycin in orbital lymphangiomas in 16 patients.

METHODS:
This prospective interventional clinical study was conducted from September 2019 to September 2021. Sixteen patients with orbital lymphangiomas, diagnosed clinically and radiologically were included in this study. Patients who had hypersensitivity to bleomycin, impaired renal function test, pulmonary problems, pregnant or lactating women, and patients who lost to follow-up were excluded from this study.

All 16 patients underwent detailed ophthalmological examination, including visual acuity, refraction, slit-lamp examination, applanation tonometry and fundus examination. Magnetic resonance imaging of the orbit was done for all patients. Systemic evaluation was also carried out along with routine blood investigations, ESR, renal and liver function tests. Serial photographs were taken and documented throughout the course of treatment and follow-up. Informed written consent was taken from all patients.

Bleomycin is commercially available in a dried powder form containing 15 international units (IU). 1 IU of bleomycin is equivalent to 1 mg of bleomycin. The dose for treatment of orbital lymphangiomas was estimated to be 0.5 IU/kg body weight and the maximum cumulative dose should not exceed 5 IU/kg body weight. Bleomycin solution was prepared with normal saline and 2% lignocaine at the ratio of 1:1. The volume injected into the lesion was proportional to the volume of the aspirate from the lesion (preferably 20% of the aspirate) but did not exceed 5 ml at a session. The procedure was done under general anesthesia for children (<18 years of age) and with topical anesthesia along with sedation for adults. The reconstituted solution was injected intralesioally using a 23-gauge needle with 10cc syringe for aspiration. For deep intraconal lesions ultrasound guided injection was
given. (Figure 1) First aspiration of the contents of the lymphangiomatous cysts was done and the fluid was sent for cytological testing. The needle was kept in the same position and bleomycin was injected keeping the total volume of the injected solution around 20% of that of the aspirate. Injection of larger volume can cause extravasation of the drug, inadequate dispersion of the drug and compressive effects. Immediately after the procedure local pressure was applied to prevent leakage of bleomycin. Pupillary reactions and visual acuity were checked for a couple of hours following injection. Patients were reviewed on the first day postoperatively and again at 2 weeks. Those who required repeat injections were treated at intervals of 4 weeks. Treatment was discontinued after a maximum of 3 injections or when no further sign of resolution was noticed clinically. MRI scan of the orbit was repeated 6 months after the last injection to document the radiological evidence of resolution or any recurrence. Patients were under follow-up upto 1 year after completion of the treatment course.

RESULTS:

In our study out of the total 16 patients, 10 were females (62%) and 6 were males (38%). Five patients were in the paediatric group (< 16 years of age). All patients had unilateral presentation. Proptosis was the most common symptom (56%), followed by lid swelling (44%). Four patients with lid swelling had associated conjunctival mass as well. Two patients with proptosis had associated squint and ptosis. Table 1 summarizes the demographic and clinical profile of the patients.

The number of bleomycin injections ranged from 2 to 4, 8 patients (50%)
had a complete resolution after 2 injections and 3 patients (19%) required 4 injections for satisfactory outcome. (Figure 2) Two patients (12%) after 3 injections resolution was noted but at follow-up at 6 months recurrence was noted. Rest three patients (19%) after giving the maximum cumulative dose no resolution was noted clinically or radiologically, hence debulking or complete surgical excision was performed. Table 2 summarizes the outcome and frequency of bleomycin injections in individual patients.

In our study immediate postoperative complications were pain at injection site, lid edema, ecchymosis and transient increase in proptosis. (Table 3) No long-term or systemic complications were noted.

**DISCUSSION:**

Lymphangiomas are benign hamartomatous lymphatic malformations most commonly seen in the head and neck region. They are thought to arise due to failure of the lymphatics to connect to the venous system, abnormal budding of lymphatic tissue, and sequestered lymphatic rests that retain their embryonic growth potential. These lymphatic rests can penetrate adjacent structures or dissect along fascial planes and eventually become canalized. These spaces retain their secretions and develop cystic components because of the lack of a venous outflow tract.

Radiologically lymphangiomas are characterized by multicystic lesions with pathognomonic fluid levels. (Figure 3) They may be isointense on T1-weighted MR imaging, but hyperintense on T2-weighted imaging with internal septations. Fat-suppressed images of the orbit are useful to highlight the presence of lymphangiomas against otherwise isointense fat.
Contrast enhancement is not seen. Absence of flow voids and enlarged feeder vessels distinguish these lesions from high-flow lesions such as infantile hemangioma and arteriovenous malformations.

Histologically, lymphangiomas are composed of dilated channels and multiple cysts lined with a single layer of endothelium. The stroma often contains lymphoid aggregates, macrophages, and fibrous septa.

Orbital lymphangiomas are usually not recognized clinically at birth but becomes evident after episodes of upper respiratory tract infection, trauma, or sudden hemorrhage into the lesion. It often impose an increased risk for the development of painful proptosis, amblyopia, strabismus and compressive optic neuropathy. Ideally surgical excision is the main stay of treatment but due the extensive infiltrative nature of the lesion complete surgical excision is dangerous as there is risk of damage to adjacent vital structures and incomplete excision can lead to recurrence. Sclerosants that have been used for orbital and extraorbital lymphangiomas include sodium morrhuate, sodium tetradecyl sulfate, ethanol, bleomycin, and doxycycline. These agents can cause pressure effect in the orbit due to the volume of the injection and the edema.

Bleomycin was first used as an antineoplastic antibiotic that was isolated from the fungus *Streptomyces verticillus* by Umezawa in 1966. Its acts by causing single- or double-strand DNA breaks and inhibition of DNA and RNA synthesis. It is also causes induction of tumor necrosis factor and apoptosis in rapidly dividing cells. Its sclerosing effect on the vascular endothelium was first observed in the treatment of malignant pleural effusions. This led
to its first use for treatment of lymphangiomas in 1977 by Yura and colleagues.\textsuperscript{14} The mechanism of action of bleomycin involves apoptosis of rapidly dividing cells and inhibition of DNA synthesis and involution of the lesion by fibrosis due to induced inflammation.\textsuperscript{2}

The solution of bleomycin is prepared by addition of 2% lignocaine along with normal saline at the ratio of 1:1. The presence of lignocaine in the solution reduces discomfort for the patient postoperatively and also facilitates the dispersion of bleomycin into the cell by making the cellular membranes more permeable.\textsuperscript{7}

There are no reports of major systemic adverse effects with the use of intralesional bleomycin in the orbit or elsewhere. Systemic side effects of bleomycin include fever, nausea, vomiting, injection site reactions, loss of appetite, weight loss, pulmonary toxicity (pneumonitis and pulmonary fibrosis), and injection site skin necrosis.\textsuperscript{13} We did not see any adverse reaction in any of our patients. Pulmonary fibrosis is dose dependent, and fatal pulmonary fibrosis occurs when cumulative dose exceeds 400 mg.\textsuperscript{1}

Gooding and Meyer described bleomycin as a potential treatment for refractory orbital lymphangiomas, showing satisfactory outcome in 4 cases.\textsuperscript{13} Kumar et al had a satisfactory response in 95% of non-orbital lymphangiomas treated with bleomycin.\textsuperscript{1} Raichura et al reported a dramatic response in 13 patients with orbital lymphangioma who were treated with intralesional bleomycin injection.\textsuperscript{2} Nuruddin et al also stated the effectiveness of intralesional bleomycin in orbital lymphangiomas.\textsuperscript{7}
In our study, the common presenting symptom was proptosis and lid swelling. 8 patients had a complete resolution after 2 injections and 3 patients required 4 injections for satisfactory outcome. Two patients after 3 injections resolution were noted but at follow-up at 6 months recurrence was seen. Rest three patients after giving the maximum cumulative dose no resolution was noted clinically or radiologically, hence debulking or complete surgical excision was performed. In our study no systemic or serious local complications were noted.

CONCLUSION:

Intraliesional bleomycin therapy is an effective and safe method of treatment of orbital lymphangioma without any significant ophthalmic or systemic side effects. It is a good alternative to surgical excision where it is not possible to remove the entire mass, and the patient is also concerned about cosmesis. It can also be used as an adjunct therapy to surgical debulking, where continuous negative pressure prevents chances of recurrence.

REFERENCES:


3. International Society for the Study of VascularAnomalies [Internet].
Classification of Vascular Anomalies [cited 2016 April 18].


5. Russin JJ, Rangel-Castilla L, Kalani YS, Spetzler RF. Surgical management, outcomes and recurrence rate of orbital lymphangiomas. JSM Neurosurg Spine 2014;2:1030.


# Table 1: Clinical Summary of Patients

<table>
<thead>
<tr>
<th>S.No</th>
<th>Age/sex</th>
<th>Laterality</th>
<th>Complaints</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 years/male</td>
<td>right</td>
<td>Lid swelling</td>
</tr>
<tr>
<td>2</td>
<td>10 years/female</td>
<td>right</td>
<td>Proptosis</td>
</tr>
<tr>
<td>3</td>
<td>10 years/male</td>
<td>left</td>
<td>Lid swelling with conjunctival swelling</td>
</tr>
<tr>
<td>4</td>
<td>8 years/female</td>
<td>right</td>
<td>Lid swelling</td>
</tr>
<tr>
<td>5</td>
<td>5 years/female</td>
<td>right</td>
<td>Proptosis with squint</td>
</tr>
<tr>
<td>6</td>
<td>34 years/male</td>
<td>left</td>
<td>Proptosis with squint</td>
</tr>
<tr>
<td>7</td>
<td>50 years/female</td>
<td>left</td>
<td>Proptosis</td>
</tr>
<tr>
<td>8</td>
<td>45 years/female</td>
<td>left</td>
<td>Lid swelling</td>
</tr>
<tr>
<td>9</td>
<td>23 years/male</td>
<td>right</td>
<td>Lid swelling with conjunctival swelling</td>
</tr>
<tr>
<td>10</td>
<td>33 years/male</td>
<td>left</td>
<td>Proptosis with conjunctival swelling</td>
</tr>
<tr>
<td>11</td>
<td>48 years/female</td>
<td>right</td>
<td>Proptosis</td>
</tr>
<tr>
<td>12</td>
<td>55 years/female</td>
<td>right</td>
<td>Proptosis</td>
</tr>
<tr>
<td>13</td>
<td>37 years/male</td>
<td>right</td>
<td>Proptosis</td>
</tr>
<tr>
<td>14</td>
<td>50 years/female</td>
<td>left</td>
<td>Lid swelling with conjunctival swelling</td>
</tr>
<tr>
<td>15</td>
<td>55 years/female</td>
<td>left</td>
<td>Proptosis</td>
</tr>
<tr>
<td>16</td>
<td>43 years/female</td>
<td>left</td>
<td>Lid swelling</td>
</tr>
</tbody>
</table>
Table 2 OUTCOMES OF INTRALESIONAL BLEOMYCIN

<table>
<thead>
<tr>
<th>S.NO</th>
<th>AGE/SEX</th>
<th>NO. OF INJECTIONS</th>
<th>OUTCOME AT FOLLOW-UP 1 YEAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 YEARS/MALE</td>
<td>2</td>
<td>COMPLETE RESOLUTION</td>
</tr>
<tr>
<td>2</td>
<td>10 YEARS/FEMALE</td>
<td>4</td>
<td>COMPLETE RESOLUTION</td>
</tr>
<tr>
<td>3</td>
<td>10 YEARS/MALE</td>
<td>2</td>
<td>COMPLETE RESOLUTION</td>
</tr>
<tr>
<td>4</td>
<td>8 YEARS/FEMALE</td>
<td>2</td>
<td>COMPLETE RESOLUTION</td>
</tr>
<tr>
<td>5</td>
<td>5 YEARS/FEMALE</td>
<td>3</td>
<td>RECURRENCE AT 6 MONTH FOLLOW UP</td>
</tr>
<tr>
<td>6</td>
<td>34 YEARS/MALE</td>
<td>4</td>
<td>COMPLETE RESOLUTION</td>
</tr>
<tr>
<td>7</td>
<td>50 YEARS/FEMALE</td>
<td>2</td>
<td>COMPLETE RESOLUTION</td>
</tr>
<tr>
<td>8</td>
<td>45 YEARS/FEMALE</td>
<td>2</td>
<td>COMPLETE RESOLUTION</td>
</tr>
<tr>
<td>9</td>
<td>23 YEARS/MALE</td>
<td>3</td>
<td>NO RESOLUTION, SURGICAL EXCISION DONE</td>
</tr>
<tr>
<td>10</td>
<td>33 YEARS/MALE</td>
<td>3</td>
<td>RECURRENCE AT 1 YEAR FOLLOW UP</td>
</tr>
<tr>
<td>11</td>
<td>48 YEARS/FEMALE</td>
<td>3</td>
<td>NO RESOLUTION, SURGICAL EXCISION DONE</td>
</tr>
<tr>
<td>12</td>
<td>55 YEARS/FEMALE</td>
<td>4</td>
<td>NO RESOLUTION SURGICAL EXCISION DONE</td>
</tr>
<tr>
<td>13</td>
<td>37 YEARS/MALE</td>
<td>4</td>
<td>COMPLETE RESOLUTION</td>
</tr>
<tr>
<td>14</td>
<td>50 YEARS/FEMALE</td>
<td>2</td>
<td>COMPLETE RESOLUTION</td>
</tr>
<tr>
<td>15</td>
<td>55 YEARS/FEMALE</td>
<td>2</td>
<td>COMPLETE RESOLUTION</td>
</tr>
<tr>
<td>16</td>
<td>43 YEARS/FEMALE</td>
<td>2</td>
<td>COMPLETE RESOLUTION</td>
</tr>
</tbody>
</table>
Table 3 IMMEDIATE COMPLICATION POST BLEOMYCIN

<table>
<thead>
<tr>
<th>IMMEDIATE POST-OP COMPLICATION</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAIN</td>
<td>39%</td>
</tr>
<tr>
<td>ECCHYMOSIS</td>
<td>22%</td>
</tr>
<tr>
<td>EDEMA</td>
<td>28%</td>
</tr>
<tr>
<td>TRANSIENT INCREASE IN PROPTOSIS</td>
<td>8%</td>
</tr>
</tbody>
</table>

Figure 1 Ultrasound guided injection of bleomycin
Figure 2 A) Pre-op Left Lymphangioma B) Post bleomycin injection twice

Figure 3 MRI ORBIT - PATHOGNOMIC FLUID LEVELS IN ORBITAL LYMPHANGIOMA
LOCAL TUMOR CONTROL BY ADJUVANT PLAQUE BRACHYTHERAPY IN CONJUNCTIVAL MELANOMA

Abstract

Purpose:

Considering high malignant potential and local tumour recurrence of conjunctival melanoma, enucleation was often performed. We assessed role of adjuvant plaque brachytherapy in a retrospective case series of 15 consecutive patients.

Results: Median age 33(range 8-65)y. Mean diameter 9.9±3.2(range 4-17)mm, mean height 2.9±1.2(range 1.5-6)mm. Corneal and scleral invasion was assessed clinically (UBM, OCT or MRI), intraoperatively and by histopathology (HPE). Ru-106 plaque brachytherapy was done at primary excision in 8(54%) or following HPE confirmation of base invasion in 7(46%) to 2-3mm depth, 10000 cGy apex dose, mean duration 37.4±18.9(range 11.5-74)h. Two patients had regional lymph node metastasis. At mean follow-up of 8.1 y, vision salvage and local tumour control
control was achieved in all, with no mortality.

**Conclusion:**

Adjuvant Ru106 plaque brachytherapy in patients with corneal and/or scleral invasion aids in preservation of the eye and vision and minimizes local tumour recurrence.

**Introduction**

 Conjunctival melanoma (CM) is a rare, aggressive pigmented ocular surface tumour accounting for 0.25% of all melanomas overall, 2% of all eye tumors and 5% of melamomas in ocular region with an incidence of 0.24 to 0.80 per million. [1–3]

Tumor staging is done based on the American Joint Committee on Cancer (AJCC) staging system. In CM there are high chances of metastasis occurring via lymphatic drainage, hematogenously and locally via the sub-epithelial space and the risk factors have been considered to be non-bulbar tumour location, multi-focality, higher AJCC stage, high baseline tumour thickness, BRAF-mutated tumour and associated ulceration.[4,5] Several treatment modalities have been practised over the years including wide excision with cryotherapy, topical chemotherapy with or without adjuvant radiotherapy (primary or secondary). Despite all efforts, CM has a local recurrence rate of 26-60% at 5 years and 38-69% by 10 years. This spikes the morbidity and mortality rates making the 5-year mortality and 10-year mortality to be 83-93% and 82-90% respectively[1] and considering these facts it is essential to know about the corneal and scleral invasion in these patients.
Enucleation used to be a necessary intervention in the patients with corneal and scleral invasion. However, the advent of plaque brachytherapy has revolutionised the treatment approaches and a multi-modal management approach can certainly help in reducing the morbidity and mortality. Therefore, this study aims at exploring the role of multi-modal treatment by surgical excision and adjuvant plaque brachytherapy in patients with conjunctival melanoma with corneal and scleral invasion.

**Methods**

A retrospective interventional case series was carried out which included patients with CM managed with wide excisional biopsy of tumour and conjunctival cryotherapy who were found to have clinical and histopathologically proven scleral or corneal invasion. Ruthenium-106 plaque brachytherapy was done for all the patients either as primary or as secondary adjuvant treatment at an ocular oncology centre in southern India between 2013-2021. Institutional review board approval was obtained and written informed consent was taken from all patients.

Patient data were extracted from medical records and included patient age at diagnosis (years), gender (male or female), presenting symptoms, carcinomas elsewhere in the body, prior ocular treatment, and lymph node involvement (submandibular, anterior cervical, or preauricular). The ocular features included best-corrected visual acuity (VA), intraocular pressure (mm Hg), tumour laterality (unilateral or bilateral), configuration (nodular, flat, papillomatous, or sessile), tumour extent, tumour multiplicity (unifocal or multifocal), tumour basal dimensions and thickness (millimeters),
corneal involvement, presence of feeder and/or intrinsic blood vessels, and associated ocular findings. The tumour basal diameter and thickness were measured clinically and with slitlamp biomicroscopy and confirmed with ultrasound biomicroscopy (UBM). All findings were documented with anterior segment drawings, slitlamp photography, anterior-segment optical coherence tomography, and UBM. Histopathologic diagnosis of CM was confirmed in all cases.

The advantages, disadvantages and the potential risks of plaque radiotherapy were discussed with the patient, and written informed consent was obtained. Each tumour was treated with a ruthenium-106 (Ru) plaque either as primary or adjuvant secondary treatment after complete surgical excision. Initial follow-up examination was performed at 6 weeks after plaque removal. Features recorded at each follow-up visit included best-corrected VA, tumour response (including basal diameter and thickness, measured by both slitlamp biomicroscopy and UBM), status of tumour, recurrence, complications from treatment, and globe salvage. Patient outcome (alive, alive with metastasis, death due to metastasis, or death due to other causes) was noted.

Results

The median patient age was 33 years (range, 8-65 years) with 7 (46.7%) males and 8 (53.3%) females. The lesions originated from primary acquired melanosis (PAM) in 7 (46.7%) and a nevus in 6 (40%) and denovo in 2 (13.3%). The most common presentation included a pigmented, elevated or flat lesion with a prominent feeder vessel and intrinsic vascularity with or
without scleral fixity and corneal invasion with assessment of the involved clock hours. At baseline the mean tumour thickness was 9.9±3.2 mm (range 4-17mm) and the mean height was 2.9±1.2 mm (range 1.5-6 mm). Corneal and scleral invasion was assessed clinically (UBM, OCT or MRI), intraoperatively and by histopathology (HPE).

Ru-106 plaque brachytherapy was done at primary excision in 8(54%) or following HPE confirmation of base invasion in 7(46%). The dosimetry was obtained by the radiation oncologist and for all the cases radiation exposure was given to 2-3mm depth with 10000 cGy apex dose for a mean duration of 37.4±18.9(range 11.5-74)hours. Two patients had regional lymph node metastasis.

Following the procedure complications included symblepharon (n = 2), scleral thinning (n = 2) and pseudopterygium formation (n = 2). These were unrelated to plaque dosage. At mean follow-up of 8.1 years (median, 7.5 years; range, 5-14 years), local tumour control was achieved in all 15 cases (100%). However, further tumour recurrence at a distant conjunctival site remote from the radiotherapy and within the globe was detected in 1 case which was managed with excision and cryotherapy. Vision salvage and local tumour control was achieved in all, with no mortality

Discussion

As per the assessment of time trend by Triay et al, the tumors became smaller and thinner over the years with a tendency to arise from the parts exposed to ultraviolet radiation [11] with a higher incidence in men and women > or = 65 years (1.48 and 1.39 cases/million, respectively) than in
younger men and women (0.3 and 0.2 cases/million, respectively).[11] We did not observe any such trend in our cases over the years and saw an equal gender distribution i.e. 7 (46.7%) males and 8 (53.3%) females.

Lommatzsch et al in 1990 stated that less recurrence occurred in the radiated patients with a 10-year survival rate of 76.3%. [6] Similarly Krause et al in 2008 studied 15 patients of CM and observed that in 8 cases there was recurrence in the non-radiated area whereas 3 developed recurrence even in the radiated area. [7] In 2009, Walsh-Conway et al concluded at a mean follow up of 23.4 months that 2 patients out of 5 developed recurrence at a site distant from the treatment site along with corneal ulcerations as complications. [8] Corneal ulcerations were also seen in 6 out of 19 cases in a study in 2010 by Karim et al. [9] A multi-centre study in 2020 by Jain et al showed a cumulative recurrence of 36.9% at a 10-years follow-up. [10] Isager et al stated that the 5-year and 10-year mortality rate was 83-93% and 82-90% respectively as per a 55-year analysis in Denmark which included 115 patients of CM. [1]

Previously done studies have shown variable usage of plaque type including strontium, yttrium, iodine and ruthenium plaque with or without histopathology assessment. Variable local recurrence was observed in the previously done studies with survival rate as 76.3% or recurrence rate of 36.9%. Ours was the first study worldwide performed by a single surgeon with 15 consecutive cases undergoing plaque brachytherapy with zero local recurrence. Multimodal treatment includes image guided assessment followed by surgical excision with 4mm clinically clear margins, lamellar sclerectomy, alcohol keratoepithelectomy, double freeze thaw cryotherapy
to edge and base thus ensuring margin and base control, adjuvant plaque brachytherapy and histopathological confirmation and in our study all the patients were alive and well by the end of a mean follow-up of 8.1 years thus achieving life and globe salvage.

**Conclusion**

Multi-modal management with adjuvant Ru106 plaque brachytherapy in patients with corneal and/or scleral invasion aids in preservation of the eye and vision and minimizes local tumour recurrence.

**References**


IMPACT OF SCREEN TIME ON OCULAR SURFACE IN CHILDREN

The average duration of daily media consumption has increased in today’s paediatric age group. The use of smartphones and tablets have become the new normal for a majority of them. Increased use of these devices often lead to a variety of asthenopic symptoms. However, the paediatric population is more tolerant to these symptoms compared to adults and many of them go undiagnosed. As such there is a strong need for a uniform protocol to screen for dry eye disease irrespective of symptoms.

Purpose

To evaluate the impact of electronic media use on ocular surface health in children. The study design was cross section observational study with purposive sampling. Children attending OPD from September 2019 to October 2020, in the age group of 5 to 15 years, who were using appropriate spectacle correction were included in the study. Exclusion criteria were children with (1) congenital abnormalities of the eye, (2) autoimmune diseases, (3) prior history of ocular surgery or trauma, (4) any pre-existing morbid ocular conditions, (5) severe allergy or severe dryness secondary to systemic illness.
A total of 78 children were included in the study. All of the children underwent comprehensive ophthalmic evaluation including best corrected visual acuity tests, biomicroscopic evaluation to detect problems of eyelids, conjunctiva and cornea. Dry eye evaluation included Schirmer testing, tear break up time and fluorescein staining. OSDI scoring was included along with the questionnaire to obtain information about pattern and duration of electronic media use and possible dry eye symptoms.

Based on the duration of screen time, the participants were categorized into 3 main groups.

A) Those with less than 1 hour of smartphone use were included in the control group. It had two subgroups with Control group 1 having less than 3 hours of other media and control group 2 having more than 3 hours of other media. B) Those with more than 1 hour of smartphone use were included in the study group. Those with less than 3 hours of other media were in study group 1 and those with more than 3 hours of other media were included in study group 2. And C) study group 3 included those with more than 4 hours of smartphone use.

RESULTS

A total of 78 children were included in the study with a mean age of 11.27±2.96. 57.70% of the study population were males. [Fig 1] Nearly 95% of the study population used smartphones with 19.2% having access to computers and television along with smartphones.
70.5% of the study population had symptoms like headache, watering, blurring of vision and burning sensation with headache being the commonest. It was observed that the percentage of symptoms increased with screen time.
The OSDI score of more than 12 was noted in 57.7% of the population. The mean increase in OSDI score from short screen time to long screen time groups showed a statistically significant change (p<0.0001).

Table 1: Comparison of Mean OSDI score

<table>
<thead>
<tr>
<th>Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 1</td>
<td>9.76</td>
</tr>
<tr>
<td>Control 2</td>
<td>15</td>
</tr>
<tr>
<td>Study 1</td>
<td>14.5</td>
</tr>
<tr>
<td>Study 2</td>
<td>17.5</td>
</tr>
<tr>
<td>Study 3</td>
<td>23.33</td>
</tr>
</tbody>
</table>

Figure 5
While none of the participants in the study showed a Schirmer value less than 11, the mean value showed a decreasing trend as the duration of screen time increased.

Tear break up time showed a statistically significant decrease from short screen time groups to long screen time groups ($p<0.0001$). Study group 3 showed a TBUT less than 10 seconds for all its members.

<table>
<thead>
<tr>
<th>Group</th>
<th>TBUT RE</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 1</td>
<td>11.04</td>
<td></td>
</tr>
<tr>
<td>Control 2</td>
<td>9.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Study 1</td>
<td>9.48</td>
<td>1.6</td>
</tr>
<tr>
<td>Study 2</td>
<td>9</td>
<td>2.2</td>
</tr>
<tr>
<td>Study 3</td>
<td>7.6</td>
<td>1.03</td>
</tr>
</tbody>
</table>

Figure 6
Positive fluorescein staining was noted in 7.7% of the population and showed a positive correlation with smartphone screen time.

**DISCUSSION**

A review of relevant literature shows other studies comparing electronic media use and ocular surface health.

<table>
<thead>
<tr>
<th>S. No</th>
<th>Article</th>
<th>Sample size (Age group)</th>
<th>Parameters</th>
<th>Conclusion</th>
<th>p - Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Jung Han Choi et al&lt;sup&gt;1&lt;/sup&gt;; 2018</td>
<td>80 (21-36 Years)</td>
<td>Smartphone use vs OSDI</td>
<td>Smartphone use aggravated OSDI score</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

![Figure 7](image-url)

348
CONCLUSION

Our study showed that a significant portion of the study population had symptoms. While the results did not indicate severe disease, both the OSDI and TBUT values showed a significant change as duration of screen time increased. Fluorescein staining was higher in groups with high media use; however, the results were not statistically significant. In this generation of ever-increasing dependency on electronic media devices, both the children and parents need to be made aware of its ill effects. As such studies like these that compare the direct effects of screen time on ocular surface health
become even more important. The small sample size and limited duration of study was a limitation in our study. However, it still shows that there is a need for more holistic diagnostic policies that can diagnose dry eye disease before their symptomatic manifestation.

REFERENCES


SAFETY AND EFFICACY OF 27-GAUGE LENS SPARING VITRECTOMY FOR STAGE 4 RETINOPATHY OF PREMATURITY

Introduction

Lens sparing vitrectomy (LSV) is the standard of care for management of stage 4 Retinopathy of Prematurity (ROP). With the advent of 27-gauge instrumentation, the advantages of smaller incision size, precise dissection and sutureless closure can potentially be transferred to eyes with ROP. We report the safety and efficacy of 27-gauge LSV in management of stage 4 ROP

Material and Methods

This was a retrospective, non-comparative, interventional case series. The study was approved by the institute ethics committee and adhered to the tenets of the declaration of Helsinki. All eyes with stage 4 ROP that underwent 27-gauge LSV between September 2019 to September 2020 were included. Pre-operative characteristics like tunica vasculosa lentis,
vascular activity, extent of fibrovascular proliferation (FVP) were noted from a pre-designed performa and RetCam images. Intra-operative events like lens touch, bleeding, retinal breaks, and operative time were also noted. Successful anatomical outcome was defined as re-attachment of the posterior pole at 3-months following surgery.

Results

Forty-four eyes of 31 infants underwent 27-gauge LSV. Mean post menstrual age at the time of surgery was 42.23 weeks. Of the infants who had both eyes operated, 10 had simultaneous bilateral surgery while 3 underwent surgery on separate days. 27 eyes had stage 4A ROP while the remaining 17 had stage 4B ROP. Majority of the eyes (18) had 3 – 6 clock hours of FVP. 42 eyes had laser prior to surgery. Anti VEGF was given pre-operatively in 7 eyes and 11 eyes had received it during the prior treatment of ROP. Vascularly active ROP was seen in 8 eyes. The mean vitrectomy time was 18.25 minutes while the mean entry and closure times were 5.38 and 5.43 minutes respectively. Sutures were required in 13 eyes. Out of 41 eyes with a minimum follow up of 3 months, favorable anatomical outcome was obtained in 30 eyes (73.17%) at a mean follow up of 8.4 months. Complications encountered were intra-operative lens touch (2 eyes), post-operative loose blood (13 eyes), cataract (3 eyes), glaucoma (2 eyes) and posterior hyaloid contracture (3 eyes).

Conclusion

27-gauge LSV appears safe and effective in the management of stage 4 ROP.
EFFECT OF CAP DEPTH ON SMILE ON CLINICAL, BIOMECHANICAL AND MOLECULAR OUTCOMES

Abstract

AIM-

To evaluate the effect of different SMILE cap depth on postoperative visual outcome, corneal nerves, healing and dry eye.

METHODS-

100 eyes (50 patients) underwent SMILE with cap depth of 100 &150 µ in contralateral eyes. Visual outcome, Epithelial remodelling, Biomechanics, Nerve changes(IVCM), tear molecular factors were analysed at 1, 3 and 6 months postoperative and compared to presurgery values.

RESULTS –

Eyes with 100 µ cap depth showed slower subbasal nerve regeneration than 150µ but recovered by 6 months. No difference noted in epithelial healing and visual outcomes. Transient dry eye noted in both groups Pre and post biomechanics evaluated. Tear molecular factors analysed shows slightly elevated inflammatory factors at 100 µ cap depth.
CONCLUSION

Different cap depths in SMILE could influence early and late postsurgical outcomes by its impact on wound healing, inflammation and biomechanics.

Introduction

Small incision lenticule extraction (SMILE) by the VisuMax femtosecond system (Carl Zeiss Meditec AG, Jena, Germany) is a flapless minimally invasive laser vision correction (LVC) for the treatment of myopia and myopic astigmatism. The stability and safety of the procedure has been studied in different studies and has been compared to other forms of LVC.\textsuperscript{1,2} An advantage of the laser platform is the ability to customize treatment parameters like the cap depth and morphology.\textsuperscript{3} The quality of vision, stability of refractive error correction, wound healing, dry eye incidence and corneal biomechanics are important parameters to study outcomes of any LVC. Changes in the epithelial thickness and wound healing after SMILE may have a bearing on this.\textsuperscript{9} Higher order aberrations like spherical aberrations were also shown to be less with deeper cap of 150 microns in another study in the early postoperative period.\textsuperscript{10} The incidence of dry eye post SMILE surgery has been shown to be less compared to LASIK in certain studies,\textsuperscript{13,14} but still needs further evaluation.\textsuperscript{15} Measuring the tear inflammatory factors give us a good indication of the causes of inflammation, irritation and pain in the eye and need for modifying therapy if required.\textsuperscript{18} These measurements reveal how the depth of ablation affects nerve related parameters and if the ablation depth increases the chances of postsurgical dry eye and inflammation. Biomechanical changes post SMILE surgery are an important
indicator of corneal strength and risk of ectasia. Varying results have been seen in studies comparing LASIK and SMILE with some showing similar results,\textsuperscript{19,20} and others better results in SMILE.\textsuperscript{21} The above described observations and literature point out an important aspect of refractive surgery, the cap depth that may affect treatment outcomes. Therefore we have proposed a comprehensive study on eyes undergoing surgery measuring the various imaging biomarkers apart from the clinical and visual parameters as well as outcomes.

**Methods**

This was a prospective interventional contralateral eye study done at a tertiary care eye hospital. The study was approved by the institutional ethics committee and was conducted as per the declaration of Helsinki. All participants gave prior written informed consent before being included in the study. 100 eyes of 50 patients who underwent SMILE with cap depth of 100 & 150 µ in contralateral eyes were included in the study. The study parameters included Visual outcome, epithelial remodelling, biomechanics, nerve changes (IVCM), tear molecular factors were analysed at 1, 3 and 6 months postoperative. These values were compared to pre-surgery values. Exclusion criteria were –

Patients not suitable for refractive surgery due to abnormal topography or excess refractive error beyond recommended limit,

Keratoconus or other corneal ectasia,

Severe aqueous deficiency dry eye or other chronic ocular surface disorder,

Corneal scarring,
Active ocular infection and
Previous ocular surgery.

Results

All patients were followed up for a period of 6 months postoperatively and their results were compared to preoperative values. At the end of 6 months all eyes included in the study achieved an uncorrected visual acuity of 6/6 or better. No eyes had a loss of lines of vision. No difference in post operative discomfort was noted between the 2 eyes. Eyes with 100 μ cap depth showed slower subbasal nerve regeneration than 150μ but recovered by 6 months. No difference noted in epithelial healing and visual outcomes. Transient dry eye was noted in both groups which recovered completely by 6 months in all patients. Pre and post biomechanics evaluated was also comparable between the groups.

Discussion

Several studies have evaluated the accuracy, precision, and reproducibility of different cap thicknesses in SMILE.\textsuperscript{4,5} However there is no conclusive evidence to decide on an ideal depth.\textsuperscript{6} In a contralateral eye study done, no statistically significant differences in the refractive outcome and higher order aberrations were reported between the depths of 100 and 160 mm,\textsuperscript{7} which was similar to the findings in this study. The depth of the cap has been shown to have a bearing on post operative refractive correction with deeper caps found to have undercorrection in high myopic correction.\textsuperscript{8} On the other hand, in another study deeper cap thickness were shown to have better recovery, less wound healing response especially in the thicker corneas.
undergoing SMILE surgery.³

A thicker cap may also cause less stromal nerve damage and therefore less dry eye, ⁸ however in this study no such difference was noted. Few studies have evaluated the relation of the cap depth with biomechanics of the cornea.²³,²⁴ Anatomically, the anterior 1/3 of the stroma has an interwoven arrangement while the posterior 2/3 has a more lamellar arrangement of fibres.²⁵ This could be responsible for the decrease in corneal strength as we go deeper into corneal stroma. No difference was seen in this study

Conclusion- Different cap depths in SMILE could influence early and late postsurgical outcomes by its impact on wound healing, inflammation and biomechanics. However at the depths specified, no significant difference was noted.

REFERENCES


4. Ganesh S, Brar S, Relekar KJ. Epithelial thickness profile changes


37. Kumar NP, Banurekha VV, Nair D, et al. Circulating angiogenic factors as biomarkers of disease severity and bacterial burden in


ACUTE ACQUIRED COMITANT ESOTROPIA PRECIPITATED BY EXCESS NEAR WORK DURING THE COVID-19 INDUCED HOME CONFINEMENT

ABSTRACT

To evaluate the causes of acute acquired comitant esotropia (AACE) in young adults and children during the COVID-19 induced home confinement. A retrospective, clinical study of patients who presented to a tertiary eye care center in South India during the COVID-19 pandemic (August 2020-January 2021) with AACE. Majority {11(73.3%)} of the total 15 patients were students >10 years of age (mean age=16.8 years). Most;12(80%) had > 8 hours of near activity/day with(mean= 8.6 hours/day). The most common near activity was online classes, followed by job related work and mobile games.86.7% used smart phones for near work. The average esotropia was 22.73 PD for distance and 18.73 PD for near. Majority (66.6%) had low-moderate hyperopia with basic or divergence insufficiency esotropia and the remaining 33.3% with myopia fitted in to the Bielschowsky type AACE. The habit of long-time sustained near work, especially on smart phones may
increase the risk of inducement of AACE.

**INTRODUCTION:**

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV2 has changed life dramatically for us; both at work and at home. Global number of workers working from home is now estimated at 558 million, corresponding to 17.4% of global employment (Berg et al. 2020, ILO 2020). Schools and colleges across the country started to shut down temporarily by the second week of March 2020, to contain the spread of the novel coronavirus¹. Around 320 million learners have transitioned to e-learning since then. The increasing use of gadgets for studies, work and leisure prompted by the pandemic has led to cropping up of many health problems in the students including weight gain, sleep disruption, and psychosocial stress². The worsening dependence on digital devices during the COVID-19 pandemic and its negative impact on student’s eye health including that of computer vision syndrome and increased risk of myopia has raised some serious concerns³.

Ever since the country wide lockdown due to Covid-19 began and with the new norm of “work, study and play from home”, we saw a substantial number of children and young adults with complaints of recent onset of squinting and diplopia coming to the Pediatric ophthalmology & Strabismus services of our hospital. This prompted us to devise this study.

Acquired non-accommodative esotropia (ANAET) is a relatively rare, distinct subtype of esotropia characterized by a non-accommodative esodeviation which can occur in older children, adults and even the elderly⁴,⁵
It can result from deterioration of existing, previously controlled, esophoria or can present acutely with diplopia when it is called acute acquired comitant esotropia (AACE)\textsuperscript{6,7}. AACE contributes to about 0.3% of childhood strabismus. AACE can be divided into five different subtypes\textsuperscript{8-12}. The Swan type (Type I) occurs after a period of interrupted binocularity\textsuperscript{9}. Type II AACE, known as Burian-Franceschetti, has minimal hypermetropia and diplopia that are often associated with physical or psychological stress\textsuperscript{10}. The Bielschowsky type (Type III) is associated with patients with myopia, convergence spasm, and divergence paralysis\textsuperscript{11}. Type IV/refractive-accommodative type is characterized by high hypermetropia that can be adequately controlled with the refractive correction alone\textsuperscript{12}. Type V, a lesser common entity, is associated with intracranial pathology, most commonly a posterior fossa lesion\textsuperscript{13}. In a small retrospective noncomparative study of 10 adult patients with acute-onset concomitant esotropia, Spierer\textsuperscript{14} found that almost all were myopic, all regained normal stereopsis after surgery and suggested that they be classified as a distinct subgroup of acute-onset esotropia.

**PURPOSE:**

To examine the causes of acute acquired comitant esotropia (AACE) in young adults and children in the setting of COVID-19 induced home confinement.

**MATERIALS & METHODS**

This was a retrospective, clinical study of all patients, who presented to the Pediatric Ophthalmology and Strabismus Services of a tertiary eye care center in South India, from August 2020 to January 2021 during the COVID-
19 pandemic, with acute-onset, comitant esotropia.

The diagnosis of AACE was made on the following criteria:

1. Acute onset of esotropia within hours/days/weeks, with photographic evidence of previously aligned eyes.
2. Age of onset after 1 year of age.
3. Comitant esodeviation with normal ocular movements.

Apart from the demographic parameters like age, sex, occupation/class of study, visual acuity for distance & near, binocular status for distance & near, amount and type of deviation were studied. A careful history including duration of presenting complaint, any precipitating event, previous use of glasses, nature, duration and medium of near work were taken. All patients underwent a meticulous ocular examination including a dilated fundus examination. Cycloplegic refraction was done with atropine in all patients to detect true refractive status and to rule out accommodative esotropia. A detailed orthoptic evaluation was also performed. Occlusion therapy was started in all children detected to have amblyopia or at risk of amblyopia. All patients underwent magnetic resonance imaging (MRI) of the brain and orbits to rule out intracranial pathology as well as a neurology evaluation. The minimum follow-up period was 6 months. The study was conducted in accordance with the Declaration of Helsinki, and was approved by the appropriate Institutional Review Board and Ethics committee.

We found 4 categories of patients with AACE in our study:

Those with myopia (SE>=-0.5DS) and divergence insufficiency (distance
esotropia > near esotropia) and occasionally equal deviation for distance and near as described by Bielschowsky\textsuperscript{11}.

Those with low hyperopia (SE\textless;=2DS) and divergence insufficiency esotropia
Those with low hyperopia (SE\textless;=2DS) and basic type esotropia (difference between distance and near esotropia not >5PD)
Those with moderate hyperopia (SE=2.25-5DS), with esotropia precipitated by stress (fever prior to onset of esotropia in our patient).

The only common factor in all these patients with esotropia was excessive near work either on smart phone, laptop or books except in one patient with low hyperopia and divergence insufficiency esotropia who denied any over use of near work.

**RESULTS**

We had total 15 cases of acute esotropia in our study; 11 males and 4 females. The age ranged from 5 years to 24 years with majority above 10 years and with a mean age of 16.8 years (SD: 5.659). Majority; 11 (73.3%) were students and the rest 4 (26.7%) were employed. Most patients (73.3%) presented with diplopia and squint, whereas 6 (40.0%) had diplopia alone and 2 (13.3%) presented with squint alone. The mean duration of presentation was 2.98 months (SD: 4.790) and ranged from 15 days to 6 months. There was no precipitating event other than excess near work in the majority except in one patient who had fever prior to the onset of esotropia. MRI of the Brain was done in all and were unremarkable, duration of near work ranged from 3-12 hours a day with a mean duration of 8.6 hours/day.
Most; 12(80%) had more than 8 hours of near activity. The near activity was related to online classes in 8 (53.3%), official work in 3 (20%), mobile games in 3 (20%) and religious text reading in 1 (6.7%) respectively. The medium of near work was mainly smart phone alone in 13 patients (86.7%), smart phone and laptop in 1 patient (6.7%) and books in 1 patient (6.7%). Most; 9 (60%) in our study had low hyperopia (SE<=2DS), 1 (6.6%) had moderate hyperopia (2.25-5DS SE) and the remaining 5 (33.3%) had myopia (SE>=-0.5DS). Seven patients (46.7%) were using glasses at the time of presentation, of which 5 (33.3%) had myopia. Three (60.0%) out of the five with myopia admitted to doing near work without glasses. Eleven patients (73.3%) had diplopia, 1 had fusion and the rest 3 were suppressed on Worth Four Dot Test (WFDT) for distance. The mean stereopsis for near was 116.67 and ranged from 40-400 arc seconds using the Randot® Stereotest. The average esotropia for distance was 22.73 Prism Diopter (PD) and ranged from 10-40 PD; whereas for near it was 18.73 PD and ranged from 2-45 PD. Orthoptic evaluation revealed average Near Point of Accommodation (NPA) of 6 (SD=1.664), average Near Point of Convergence (NPC) of 5.36 (SD=1.689), average Negative Relative Accommodation (NRA) of 3.33 (SD=1.033), average Monocular Estimation Method (MEM) of 0.76 (SD=0.305) and an average Accommodative Convergence/Accommodation (AC/A) ratio of 5.40 (SD=3.638). There was high Positive Relative Accommodation (PRA>3.5) in 8 (53.3%) and the rest had normal (PRA<=3.5) values. Reduced or poor Negative Fusional Vergence (NFV) for distance was seen in 40% patients. On accommodative facility testing; 26.66% complained of difficulty in clearing plus lenses, 13.33% had
difficulty clearing minus lenses, 46.66% had reduced binocular accommodative facility and only 2(13.33%) had normal facility. Most of those with myopia (3 out of 5) had high AC/A ratio, accommodative lag (4 out of 5) on MEM but had esodeviation more for distance than near contrary to the expectation. All 5(33.33%) of those with myopia fitted in to the Bielschowsky type of AACE with 4 of them having divergence insufficiency and the remaining 1 having basic type AACE. One patient with moderate hypermetropia and diplopia, had fever preceding the onset of esotropia, was prescribed plus lenses and could be classified as Burian-Franceschetti type of AACE. The remaining 9(60%) had low hyperopia with either basic type AACE (33.3%) or divergence insufficiency type AACE (26.7%). All were advised to restrict and reduce their near work, those with glasses were advised constant use and those with divergence insufficiency were prescribed divergence exercises or prisms. Reduction of near work with divergence exercises was helpful in 5 patients in our study. Those with basic type AACE, who did not improve were advised squint surgery. Ground prisms in glasses were prescribed for 2 patients, both with myopia and divergence insufficiency type AACE(3 PD BO OU & 6 PD BO OD respectively). Four patients; 3 with low hyperopia and basic type AACE and 1 with Burian-Franceschetti type of AACE underwent squint surgery and regained binocular vision (Figures 1 a, b, 2a, b, 3a, b,4a,b) and Tables 1 & 2.

DISCUSSION

Continuing school closure, home confinement and work from home policies during the current COVID-19 lockdown have ushered in important lifestyle
behavior changes in the young population, including a significant increase in screen time\textsuperscript{15}, digital eye strain and raised serious concerns of worsening the global burden of myopia\textsuperscript{3}. Apart from these, the excessive application of near vision might have other undesirable effects, including development of acute acquired concomitant esotropia. Lee et al\textsuperscript{16} documented a series of 12 teenagers with acute acquired concomitant esotropia who used smartphones more than 4 hours a day. Interestingly, the esodeviation improved in all patients after refraining from smartphone use for 1 month. Nevertheless, strabismus surgery was required in 5 patients with good postoperative outcomes in terms of ocular alignment and stereo acuity. The average duration of smartphone use in their study was 6.08 ± 1.78h/day, which was similar to 8.6h/day of near work in our study. In a retrospective study of 26 cases with AACE over 20 months; Yan Wu et al\textsuperscript{17} deduced that AACE could be caused by excessive near work regardless of whether or not one wears glasses regularly especially for individuals with myopic refractive error. The only common factor that contributed to the development of AACE in their study was also the excessive near visual activities, especially the use of smartphones.

In our study, majority (66.6%), had low hyperopia with basic or divergence insufficiency esotropia and the remaining 33.3% had myopia which fitted in to Bielschowsky type AACE. Excessive near work and a naturally stronger convergence in the young could have led to an imbalance between accommodation and vergences resulting in dynamic activation of the medial rectus muscles and a manifest esodeviation. This effect is greater in hyperopes due to their greater accommodative demand as also seen in our
study with 66.7% having hypermetropia. Conventionally, it is thought that the presence of myopia is associated with a decreased demand for accommodation and hence lower convergence and a predisposition for developing exotropia. However, those with myopia, can also develop esotropia due to the excessive application of near work resulting in increased tone of medial rectus muscles and coupled with the lack of distant stimuli during the home confinement leading to divergence weakness was also seen in our study. Bielschowsky\textsuperscript{11} claimed that uncorrected myopia led to the development of increased tonus of the medial rectus muscles and suggested that the increase in tonus can be explained by the tendency of individuals with uncorrected myopia to hold print or sewing excessively close to the eyes, with resulting development of esotropia. 60% of those with myopia in our study also admitted to doing near work without glasses as they felt they could see clearly. In a well-defined study of adult patients with acute-onset concomitant esotropia by Sprier et al\textsuperscript{14}, almost all were myopic, and all regained normal stereopsis after surgery. In a retrospective, clinical study of all patients under the age of 18 years with acute onset, non-accommodative comitant esotropia, we\textsuperscript{18} had earlier reported that prompt amblyopia therapy and timely surgery can result in a satisfactory outcome in those without systemic involvement. In our present study also, reduction of near work with divergence exercises was helpful in 5 patients. Two patients were given prism glasses, 4 underwent squint surgery, 3 were advised glasses and squint correction and 1 was awaiting squint surgery. All who underwent squint surgery regained binocularity and were diplopia free. Aldo Vagge et al\textsuperscript{19} described four cases of acute acquired concomitant
esotropia that occurred during the COVID-19 lockdown in Italy in 2020, wherein all patients spent 8 to 10 hours a day using computers, tablets, and smartphones to play, access school lessons, and navigate social networks. In a similar case setting of COVID-19 induced home confinement, we are reporting a case series of 15 patients with AACE.

Although the etiology of acute acquired concomitant esotropia is still debated, it has been associated with sustained near point demands due to the excessive use of computers, tablets, and smartphones. With the increasing use of smartphones and tablets in modern life, more and more work is being done through small screens at a close distance. We feel that this excessive near work, a naturally stronger convergence and lack of distance stimuli could have led to an imbalance between accommodation and vergences, resulting in dynamic activation of the medial rectus muscles with or without divergence weakness, thus producing a manifest esotropia in our patients. We feel that sustained near work played a pivotal role in the development of esotropia in our patients and hope that authorities would take serious note of this undesirable effect. Regulating the duration of e-learning, reducing the number of total hours of screen time, shifting to widescreen visual display devices like television, taking breaks, promoting healthy life style habits like increasing outdoor play should be recommended to improve the eye health of the young population.

**CONCLUSION:**

The habit of long-time sustained near work, especially on smart phones may increase the risk of inducement of AACE. Parents and public health
authorities should take serious note of this negative impact on the eye health of the young population and should bring out suitable recommendations and regulations to mitigate this undesirable effect.

REFERENCES


19. Aldo Vagge, MD, PhD; Giuseppe Giannaccare, MD, PhD; Fabio Scarinci, MD, PhD; Andrea Cacciamani, MD; Marco Pellegrini, MD; Federico Bernabei, MD; Vincenzo Scorcia, MD; Carlo E. Traverso, MD; Donatella Bruzzichessi, MD. Acute Acquired Concomitant Esotropia From Excessive Application of Near Vision During the COVID-19 Lockdown. J Pediatr Ophthalmol Strabismus. 2020; 57:e88-e91.

APPENDIX: FIGURES

Figure: 1(a) - Patient A at 1.5 years. Figure: 1(b) - Patient A (PUBG addict) before & after surgery

Figure: 2(a) - Patient B 6 months before with straight eyes. Figure: 2(b) - Patient B Class X student with 8 hours/day of online classes on smart phone; with basic type esotropia Left eye before and straight eyes after surgery
Figures: 3(a) - Patient C (using smartphone for online classes and games > 8 hours/day); showing basic type esotropia Right eye, 3(b) - Patient C showing straight eyes post Right eye surgery (Medial Rectus recession+ Lateral Rectus resection).

Figure: 4(a) Patient D before: 17 year old, college student who developed AACE with >8 hours of near work on smartphone; Figure: 4(b) Patient D
after surgery (Medial Rectus Recession + Lateral Rectus Resection)

**Table 1: Clinical Profile of Patients with AACE**

**Table 2: Features of Esotropia**

<table>
<thead>
<tr>
<th>Esotropi</th>
<th>Esotropi</th>
<th>Ty</th>
<th>Wfdt</th>
<th>Stereo</th>
<th>Refr</th>
<th>Impression</th>
<th>Mr</th>
<th>Impro</th>
<th>Otte</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 BO</td>
<td>5 BO</td>
<td>ET</td>
<td>DIPLO</td>
<td>60</td>
<td>MYOP</td>
<td>HIGH</td>
<td>nor</td>
<td>NO</td>
<td>3</td>
</tr>
<tr>
<td>40 BO</td>
<td>45 BO</td>
<td>BA</td>
<td>DIPLO</td>
<td>140</td>
<td>LOW</td>
<td>NORMAL</td>
<td>nor</td>
<td>NO</td>
<td>OO</td>
</tr>
<tr>
<td>30 BO</td>
<td>30 BO</td>
<td>BA</td>
<td>RIGHT</td>
<td>400</td>
<td>LOW</td>
<td>HIGH</td>
<td>nor</td>
<td>NO</td>
<td>(OD)</td>
</tr>
<tr>
<td>35 BO</td>
<td>30 BO</td>
<td>BA</td>
<td>DIPLO</td>
<td>CANN</td>
<td>LOW</td>
<td>HIGH</td>
<td>nor</td>
<td>NO</td>
<td>(OS)</td>
</tr>
<tr>
<td>16 BO</td>
<td>9 BO</td>
<td>ET</td>
<td>ALT</td>
<td>40</td>
<td>LOW</td>
<td>NORMAL</td>
<td>nor</td>
<td>NO</td>
<td>Diver</td>
</tr>
<tr>
<td>10 BO</td>
<td>2 BO</td>
<td>ET</td>
<td>DIPLO</td>
<td>60</td>
<td>LOW</td>
<td>LOW</td>
<td>nor</td>
<td>NO</td>
<td>Glasse</td>
</tr>
<tr>
<td>30 BO</td>
<td>30 BO</td>
<td>BA</td>
<td>DIPLO</td>
<td>140</td>
<td>LOW</td>
<td>LOW</td>
<td>NO</td>
<td>GLAS</td>
<td></td>
</tr>
<tr>
<td>25 BO</td>
<td>30 BO</td>
<td>BA</td>
<td>DIPLO</td>
<td>100</td>
<td>MYOP</td>
<td>HIGH</td>
<td>nor</td>
<td>NO</td>
<td>Glasse</td>
</tr>
<tr>
<td>12 BO</td>
<td>2 BO</td>
<td>ET</td>
<td>DIPLO</td>
<td>MYOP</td>
<td></td>
<td>NORMAL</td>
<td>nor</td>
<td>YES</td>
<td>6</td>
</tr>
<tr>
<td>35 BO</td>
<td>40 BO</td>
<td>BA</td>
<td>ALT</td>
<td>CANO</td>
<td>MOD</td>
<td>HIGH</td>
<td>nor</td>
<td>NO</td>
<td>(OU)</td>
</tr>
<tr>
<td>10 BO</td>
<td>5 BO</td>
<td>ET</td>
<td>DIPLO</td>
<td>100</td>
<td>MYOP</td>
<td>NORMAL</td>
<td>NO</td>
<td>YES</td>
<td>Glasse</td>
</tr>
<tr>
<td>25 BO</td>
<td>14 BO</td>
<td>ET</td>
<td>DIPLO</td>
<td>100</td>
<td>LOW</td>
<td>LOW</td>
<td>nor</td>
<td>NO</td>
<td>Glasse</td>
</tr>
<tr>
<td>16 BO</td>
<td>6 BO</td>
<td>ET</td>
<td>FUSIO</td>
<td>60</td>
<td>MYOP</td>
<td>HIGH</td>
<td>No</td>
<td>YES</td>
<td>Glasse</td>
</tr>
<tr>
<td>20 BO</td>
<td>8 BO</td>
<td>ET</td>
<td>DIPLO</td>
<td>100</td>
<td>LOW</td>
<td>LOW</td>
<td>nor</td>
<td>NO</td>
<td>Glasse</td>
</tr>
<tr>
<td>25 BO</td>
<td>25 BO</td>
<td>BA</td>
<td>DIPLO</td>
<td>100</td>
<td>LOW</td>
<td>NORMAL</td>
<td>nor</td>
<td>NO</td>
<td>Squin</td>
</tr>
</tbody>
</table>
Abbreviations used:

ET: ESOTROPIA

AC/A: ACCOMMODATIVE CONVERGENCE/ACCOMMODATION

MEM: MONICULAR ESTIMATION METHOD

PRA: POSITIVE RELATIVE ACCOMODATION

NRA: NEGATIVE RELATIVE ACCOMMODATION
Dr. MEHUL SHAH
MS ophthal, Fellow SN
Vitreo Retina and Ocular Trauma
General Secretary Ocular Trauma Society of India
Drashti Netralaya, Dahod, Gujarat

NEW MODEL FOR THE PREDICTION OF VISION-RELATED OUTCOMES IN YOUNG CHILDREN WITH MECHANICAL OCULAR CONDITIONS AND COMPARISON WITH OTHER MODELS

Key Message:

1. What was known? POTS is useful predictive model based on presenting vision

What is new in this paper?

1. TOTS is sensitive and specific predictive model based on clinical findings.
2. This model is accurate in case of lower risk trauma

Purpose:

Herein, we compared the efficacy among the OTS, POTS, and TOTS for prognosis prediction in Indian children who had mechanical ocular conditions causing traumatic cataract.
Methods:

This prospective, interventional study recruited consecutive children undergoing operation for traumatic cataracts caused by mechanical eye injuries at Drashti Netralaya. The following details were obtained from medical files: the circumstance and time of injuries, penetrating injury type, initial and final visual acuity (VA), time of operation, and associated eye diseases. Specific variables were employed to determine the OTS, TOTS, and POTS. For all patients, the final and predicted VA determined using all scores were compared using Fisher’s exact test; the accuracy, specificity, and sensitivity were evaluated for all scores by using the AUROC.

Results:

We enrolled 124 eyes. Patients’ mean value for age was 4.6 ± 1.29 years; 44 (35.41%) and 74 (64.5%) were female and male patients, respectively. Visual outcomes significantly improved after operation, and the outcomes did not differ between closed- and open-globe injuries (P = 0.162). The actual and predicted VA did not exhibit a statistically significant difference among the three scores. The TOTS and POTS were more suitable for evaluating low-risk injuries, whereas the OTS could more efficiently examine high-risk cases.

Conclusion:

The TOTS and POTS were more accurate than the OTS in VA prediction after operation in toddlers with traumatic cataracts caused by mechanical globe injury. All the examined scores can be helpful in estimating VA following
treatment.

**Key words:**

OTS; POTS; TOTS; BETTS; TRAUMATIC CATARACT; PAEDIATRIC OCULAR TRAUMA

**Synopsis:**

This TOTS is calculated based on clinical findings and not on presenting vision and tested for sensitivity and specificity for prediction, compared with POTS and OTS

**Introduction**

Ocular trauma does not receive adequate attention in many areas globally owing to poor infrastructure, untrained human resources, and variable outcomes. General ophthalmologists are the first-line health workers treating this eye condition, they are not particularly trained. Thus, the first assessment is performed by a relatively untrained team (REF LAJO).

Paediatric ocular trauma might result in life-long visual disability, thus posing a burden to the healthcare system and society.[1] In children, open-globe injury is regarded as the most severe eye trauma caused by the penetration of a sharp object.[2] To optimise outcomes, careful evaluation and timely treatment are vital in open-globe injury. Precise visual prognosis is a key challenge in eye trauma treatment in paediatric cases. Parents frequently question physicians whether their children would become blind or can see again. Different scoring methods available for ocular trauma evaluation can help healthcare providers appropriately predict vision-
related outcomes. The Ocular Trauma Score (OTS) is one such generic instrument used to evaluate outcomes. In this scoring methodology, visual acuity (VA) is estimated by subtracting raw points for five diagnostic findings from initial VA. However, the OTS demonstrated a low accuracy in children owing to its inability to obtain accurate VA; thus, instruments specifically for paediatric patients should be developed. The Paediatric Penetrating Ocular Trauma Score (POTS) involves the exclusion of the initially calculated VA and afferent pupil defect serving as prognostic factors and the inclusion of wound location and age as new variables. However, POTS’s drawbacks have been reported.

Ocular trauma can result in the development of cataracts. Various methodologies can be employed to determine vision-related outcomes in cataracts caused by trauma or other factors. However, in those with traumatic cataracts, damage caused to adjacent ocular tissues can possibly reduce visual gain following surgery. This phenomenon can result in different rates of success between patients with and without traumatic cataracts. Moreover, the vision-related outcomes of paediatric traumatic cataract cases are often unsatisfactory owing to recurrent inflammation and amblyopia.

The Birmingham Eye Trauma Terminology System (BETTS) provides standardised definitions for ocular trauma. These definitions can be employed to compare vision-related outcomes after operation for traumatic cataract and identify determinants that can predict the aforementioned outcomes. Most studies investigating the vision-related outcomes of traumatic cataracts have included a small sample size or were designed...
as case studies.

The Toddler/Infant OTS (TOTS) was recently designed for children aged <6 years with open-globe injury resulting from trauma. In line with the POTS, the TOTS does not rely on VA and was beneficial for prognosis prediction in US toddlers and infants.[14,15]

Methods:

This prospective cohort study was approved by the Drashti Netralaya ethics committee. (Ref-DN/2020/13) All procedures followed the tenets of the Declaration of Helsinki and its amendments.

We included all patients aged <6 years who had traumatic cataracts resulting from ocular trauma and presented at the Drashti Netralaya between January 2011 and December 2020. We excluded children with a follow-up duration of <6 months. We reviewed patients’ electronic medical records. Data retrieved included demographic factors, ocular trauma characteristics and clinical data in the pretested online format, VA at the final follow-up, and existence of concomitant ocular disease. Information for the following additional signs and ocular comorbidities used to calculate scores was collected: hyphema, iris organic/unclean injury, prolapse, detachment of the retina, vitreous haemorrhage, traumatic cataract delay of >48 h for surgery, and endophthalmitis.

We determined the OTS by using the standard table of raw points and points deducted according to comorbidities by converting them into different OTS categories.
Furthermore, the POTS was determined following the method reported by Acar et al and Shah et al.\cite{8} We assigned raw points to VA calculated at the presentation. Additional points were added or subtracted for wound location, age, and any of the eight concomitant eye conditions. For patients with missing information regarding initial VA in medical records, the following equation was adopted for trauma score calculation: $VA = 2 \times (age + zone) - \text{corresponding pathologies}$.

We stratified open-globe injuries into three anatomical zones based on their location: zone I (those confined to the limbus and cornea), zone II (those located 5 mm posteriorly to the limbus), and zone III (if the wound was extended to the macula and optic nerve posteriorly to zone II).\cite{15} The range of the resulting score was from 1 (low prognosis) to 5 (favourable prognosis).

The following injury-related characteristics were evaluated to determine the TOTS: wound size >6 mm, existence of hyphema, cataract or lens damage, choroidal detachment, and detachment of the retina; these characteristics were assigned 1, 1, 1, 2, and 1 point, respectively, and zones II and III were assigned 1 and 2 points, respectively.\cite{14} We considered the injury as having low (favourable prognosis) and high (poor prognosis) risk if the sum of points was 0 or 1 and ≥2, respectively.\cite{14}

The OTS categories 1–5 and POTS 1–5 were calculated according to vision improvements. We compared the results of OTS categories 1–5 with those of TOTS categories 5–1 and those of POTS categories 1–5 with those of TOTS categories 5–1 by using Fisher’s exact test and Student’s t test with 95% CIs.
A P value of <0.5 was considered significant.

The ROC curves comparing the TOTS with the OTS and the POTS with the TOTS for all categories were plotted to examine their specificity and sensitivity.

To perform statistical analysis, POTS and OTS categories 2–5 were all merged into the low-risk category corresponding to the TOTS category 1. The scoring methods’ predictive values were examined through a comparison of final and predicted VA by using Fisher’s exact test of independence; the sample t test was performed to evaluate its association. Specificity and sensitivity with 95% CIs were calculated using the ROC curve for each score. A P value of <0.05 indicated significance.

RESULTS:

Of 1630 traumatic cataract cases included, 457 (28%) and 1173 (72%) were female and male patients, respectively. Furthermore, 681 (41.8%) were paediatric cases.

We studied 124 patients aged <6 years; among them, 44 (35.41%) and 74 (64.5%) were female and male patients, respectively (Table 1). Furthermore, the patients’ mean and median ages were 4.6 ± 1.29 years and 5 years, respectively. Among 124 patients, 29 (23.4%) and 95 (76.6%) had closed-globe and open-globe injuries, respectively. The pre- and post-vision differed significantly. The outcomes of open-globe injury did not differ significantly from those of closed-globe injury (P = 0.162). Moreover, children aged <2 years had significantly poorer outcomes.
The number and percentage of cases with POTS and OTS categories 1–5 and TOTS categories 5–1 (more to less severe) were determined.

The difference among OTS, TOTS, and POTS categories was nonsignificant (Table 2)

No significant difference was noted between the low-risk TOTS categories and the merged 2–5 categories of POTS (P = 0.241 and 0.241, respectively; Table 2).

Sensitivity and specificity for TOTS compared to OTS and POTS is displayed in Table-3 (for merged low risk categories) and Figure-2. (For individual categories)

**Discussion:**

This study investigated the applicability and validity of TOTS, OTS, and POTS in patients aged from 0 to 6 years. The findings indicated the higher applicability of the OTS than the POTS in general population.

The OTS provides a more accurate prediction of vision-related outcomes. Nevertheless, the inclusion of children in a database of >2500 patients with severe eye injury based on which the score was formulated remains unclear [5, 6].

Although studies have employed regression tree, its validity is not evaluated. Compared with regression tree analysis, the OTS provided a highly accurate prognosis prediction (8, 9, 10).

A study developed a predictive model for open-globe injuries (9).

Another study developed the Basic Severity Score for Common Ocular
Emergencies for examining the severity status of 86 common eye conditions by using the Delphi method. In this methodology, the severity was rated using a scale (7 point) in the first round of the survey. The final severity of each item was determined according to the median ratings obtained in the final Delphi survey. However, this score is not used widely and remains to be validated (11).

Politzer et al developed the Craig Hospital Eye Evaluation Rating Scale (CHEERS) to investigate the severity and frequency of deficits in eye movements in traumatic brain injury patients (12).

Lesniak and Bauza (13) found that in paediatrics patients, the final calculated VA did not significantly differ from the VA predicted with the OTS. Sharma suggested that the initially calculated OTS might predict the prognosis of paediatric penetrating eye injury patients (14). However, Unver (15) indicated the limitation of OTS in predicting vision-related outcomes in paediatric cases (15).

Studies have prospectively validated the OTS in children (15, 16).

Bunting, Schörkhuber, Hossain, Uysal Y, and Tok have indicated that the OTS exhibited high validity in paediatric open-globe injury cases (17-21).

The OTS could predict vision-related outcomes after operation in 354 traumatic cataract patients [22]. However, the likelihood of amblyopia should be considered in children. Refractive errors, strabismus, and ocular opacity can result in amblyopia. Not including amblyopia while calculating scores can reduce OTS’s prediction accuracy. Therefore, we considered amblyopia in the OTS calculation for establishing a model for the POTS. We
validated this model and compared prediction accuracy between the OTS and POTS for evaluating outcomes in paediatric traumatic cataract patients (23, 24).

A study conducted in India validated the OTS in 787 traumatic cataract individuals [19].

Because of difficulty in obtaining RAPD and initial VA, two crucial factors for OTS calculation, in paediatric trauma patients, particularly younger children, the calculated OTS would be inaccurate. Two studies conducted in Turkey calculated the OTS for children; however, these studies reported contradictory findings [25,26]. The POTS was recently developed for prognosis prediction in children whose initial vision findings were inaccurate [23].

In children, the POTS was more accurate than the OTS, as indicated by the AUROC (23).

The accuracy of POTS and OTS in examining the prognosis of open-globe injuries in paediatric cases was similar (28).

Zhu found that the POTS was more robust than the OTS in examining penetrating injuries (29).

The findings of regression analysis revealed that both OTS and CART were robust in predicting prognosis; however, the OTS demonstrated a greater accuracy. Thus, the OTS could be employed to counsel patients and make treatment-related decisions (8).

This study examined the scoring methods’ applicability and validity. The OTS
but not the POTS demonstrated increased applicability in general population. Future studies should examine TOTS’s applicability.

To our knowledge, no study has compared the validity among the TOTS, POTS, and OTS.

In line with the BETTS, the OTS could be easily used to evaluate both closed-globe and open-globe eye injury. The examination of six factors (A to F) for prediction required for OTS calculation is relatively easy. The OTS could accurately predict vision-related outcomes in open-globe injury. However, a 1-in-5 risk of obtaining an incorrect score exists; thus, this score should not be employed to plan the primary treatment procedure. The OTS should be adopted for making treatment-related decisions (30,31). The TOTS and POTS exhibited limitations in those with poor prognosis.

Sarah et al developed a new prognostic score. Patients aged 0–6 years with open-globe injury exhibit specific risk factors indicating poor outcomes. The score calculated using our algorithm did not rely on VA acuity and thus can be beneficial for prognosis prediction in younger children (32).

**Conclusion:**

TOTS, as a novel predictive score, is more reliable than the POTS but less specific and sensitive in high-risk (OTS-1 and POTS-1) cases. The TOTS can be employed to examine outcomes in toddlers in whom vision check-up is not possible on presentation.

**References:**

1. Khatry SK, Lewis AE, Schein OD et al. The epidemiology of ocular


16. Oiticica-Barbosa MM (1), Kasahara N (2) Eye trauma in children


30. Robert scott the ocular trauma scott community eye health journal | volume 28 issue 91 | 2015


32. Read SP, Cauvoto KM. Traumatic open globe injury in young pediatric patients: characterization of a novel prognostic score. J AAPOS 2016; 20:141-144

Table 1 Age and sex distribution

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>SEX</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3-6</td>
<td>40</td>
<td>75</td>
</tr>
<tr>
<td>TOTAL</td>
<td>44</td>
<td>80</td>
</tr>
</tbody>
</table>

Table 2 Comparative study of OTS, POTS and TOTS for various trauma score categories

<table>
<thead>
<tr>
<th>VARIABLE1</th>
<th>VARIABLE2</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTS1</td>
<td>TOTS5</td>
<td>NA</td>
</tr>
<tr>
<td>OTS</td>
<td>TOTS</td>
<td>Value</td>
</tr>
<tr>
<td>------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>POTS1</td>
<td>TOTS5</td>
<td>NA</td>
</tr>
<tr>
<td>OTS2</td>
<td>TOTS4</td>
<td>0.035</td>
</tr>
<tr>
<td>POTS2</td>
<td>TOTS4</td>
<td>0.374</td>
</tr>
<tr>
<td>OTS3</td>
<td>TOTS3</td>
<td>0.242</td>
</tr>
<tr>
<td>POTS3</td>
<td>TOTS3</td>
<td>0.242</td>
</tr>
<tr>
<td>OTS4</td>
<td>TOTS2</td>
<td>0.090</td>
</tr>
<tr>
<td>POTS4</td>
<td>TOTS2</td>
<td>0.090</td>
</tr>
<tr>
<td>OTS5</td>
<td>TOTS1</td>
<td>0.065</td>
</tr>
<tr>
<td>POTS5</td>
<td>TOTS1</td>
<td>0.065</td>
</tr>
</tbody>
</table>
Table 3: Study of sensitivity and specificity of different trauma categories (Area under curve)

<table>
<thead>
<tr>
<th>TEST CATEGORY</th>
<th>AREA UNDR CURVE</th>
<th>INFEERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROC OTS POTS HIGHER RISK VS TOTS</td>
<td>000</td>
<td>TOTS IS LESS RELEVANT</td>
</tr>
<tr>
<td>ROC OTS POTS LOWER RISK VS TOTS</td>
<td>250</td>
<td>MORE SENSITIVE AND SPECIFIC</td>
</tr>
<tr>
<td>ROC OTS 2 POTS2 VS TOTS 4</td>
<td>250</td>
<td>MORE SENSITIVE AND SPECIFIC</td>
</tr>
<tr>
<td>ROC OTS3 POTS3 VS TOTS3</td>
<td>833</td>
<td>MORE SENSITIVE AND SPECIFIC</td>
</tr>
<tr>
<td>ROC OTS 5 POTS5 VS TOTS1</td>
<td>500</td>
<td>LESS SENSITIVE AND SPECIFIC</td>
</tr>
</tbody>
</table>
CORRELATING THE VEGF LEVELS WITH THE PROMPT CLINICAL REGRESSION OF TUBERCULAR GRANULOMAS

ABSTRACT

Purpose:

To report pre and post treatment levels of VEGF-A in the aqueous humour of patients with intraocular tubercular granulomas and study the effect of a combined intravitreal anti-VEGF bevacizumab and moxifloxacin therapy on their regression.

Methods:

Aqueous samples of 10 consecutive patients with intraocular tubercular granulomas obtained before and after initiating treatment were subjected to ELISA for analysing intraocular VEGF-A levels. Intravitreal injections of bevacizumab and moxifloxacin were given weekly till complete regression of these granulomas. All patients received the usual four-drug ATT and oral corticosteroids.
Results:

Mean baseline VEGF-A level was 1004.27±411.40 pg/ml (401.32-1688.95) that reduced significantly to 27.62±46.86 pg/ml (6.9-131.83) at the last injection. Mean number of intravitreal injections was 3.1 (2-4). We found significant correlation of decreasing levels of aqueous VEGF-A with the clinical regression of these tubercular granulomas.

Conclusions:

Anti-VEGFs along with moxifloxacin may be beneficial as an adjunct to ATT for a prompt regression of TB granulomas. More frequent than monthly injections maybe required due to much higher levels of VEGF in these patients.

Abbreviations:

TB: Tuberculosis; IOTB: Intraocular tuberculosis; VEGF: Vascular endothelial growth factor; RD: Retinal detachment; Mtb: Mycobacterium tuberculosis; ATT: Antitubercular therapy; AMD: Age-related macular degeneration; SRF: Subretinal fluid; ELISA: Enzyme immunosorbent assay; PCR: Polymerase chain reaction; ONH: Optic nerve head; MDR-TB: Multidrug-resistant tuberculosis; pg/ml: picogram/milliliter; ESR: Erythrocyte sedimentation rate; CECT: Contrast enhanced computed tomography; DNA: Deoxyribonucleic acid; RNA: Ribonucleic acid; BSL: Biosafety level; BCVA: Best corrected visual acuity; HM: Hand movements; KP: Keratic precipitates; PSC: Posterior subcapsular cataract; PS: Posterior
synechiae; CRA: Chorio-retinal atrophy; IVMP: Intravenous methyl prednisolone; OCT: Optical coherence tomography; RPE: Retinal pigment epithelium; FFA: Fundus fluorescein angiography; ICG: Indocyanine angiography; RAP: Retinal arterial proliferans.

Tubercular granulomas are the most well recognized pheno-type of intraocular tuberculosis (IOTB), and present as yellow-ish subretinal elevated lesions often accompanied by an exudative retinal detachment (RD). In experimental models of IOTB, these granulomas were found to show overexpression of vascular endothelial growth factor (VEGF).

It has been proposed that increased levels of VEGF may be responsible for the vascularization of these granulomas. Moreover, pharmacological inhibition of the VEGF pathway may limit the spread of *Mycobacterium tuberculosis* (*Mtb*) infection causing regression of the new vessels, and thus forms the basis of newly emerging concepts in considering host directed therapies over the usual pharmacological anti-tubercular therapy (ATT) that has been the standard of care for over six decades.

The use of ATT and oral corticosteroids in the management of tubercular granulomas has been well documented in the past. In recent years, a number of case reports have reported successful use of anti-VEGF therapy along with the standard care in the treatment of tubercular granulomas.

To the best of our knowledge, pre- and post-treatment levels of VEGF-A in the aqueous humour of patients with tubercular granulomas have not been studied. We report pre and post treatment results of VEGF-A levels in 10 consecutive patients with intraocular tubercular granulomas who showed a
prompt regression with weekly intravitreal injections of anti-VEGF bevacizumab and moxifloxacin along with the usual standard of care ATT and oral corticosteroids. A correlation was done of their clinical regression with the intraocular aqueous levels of VEGF-A.

Material and methods

All consecutive patients between January 2017 and January 2020 who presented with intraocular tubercular granulomas at the uvea clinic of a tertiary eye care hospital in North India were included in the study. All these patients met the diagnostic criteria for IOTB according to the classification by Gupta et al.13 The institutional ethics committee approval was obtained and the study adhered to the tenets of the Declaration of Helsinki. An informed written consent was obtained from all the patients. A detailed history of any exposure to pulmonary tuberculosis (TB) was taken. All patients underwent complete hemogram with erythrocyte sedimentation rate (ESR), Mantoux test, contrast enhanced computed tomography (CECT) of the chest and other relevant laboratory investigations to rule out other infectious etiologies. A thorough systemic examination was carried out by an in-house physician. Optical coherence tomography (OCT) and color fundus photo were done at baseline and after every injection. Fundus fluorescein angiography (FFA) and indocyanine green angiography (ICGA) were performed at the discretion of the treating clinician. All the patients were treated with intravitreal injection of anti-VEGF bevacizumab (1.25 mg/0.05 ml; off label use) and moxifloxacin (500 μg/0.1 ml; off label use) under topical anesthesia and aseptic precautions, along with four drug ATT and
oral corticosteroids (1–1.5 mg/kg/day). Weekly intravitreal injections were continued till there was a clinical regression of the granulomas and complete resorption of the subretinal fluid (SRF) on OCT. Complete regression of the granuloma was defined as flattening of the granuloma with normalization of the contour of the overlying retinal layers with or without chorio-retinal atrophy (CRA) and resorption of the overlying SRF. Patients who were already receiving ATT therapy for pulmonary or extrapulmonary TB were not excluded from the study.

Anterior chamber paracentesis of the aqueous fluid (0.1 ml) was done immediately after injecting the drugs, thereby normalizing the intraocular pressure. The aqueous fluid sample thus collected in a sterile syringe was packed, labelled and then transported in an insulated box with dry ice to the laboratory. The samples were subjected to sandwich enzyme immunoassay (ELISA) for analyzing intraocular VEGF-A levels. VEGF-A levels were calculated by using human VEGF anti-body pair kit {Invitrogen; 10 plate Format; Lot#: 650073; Catalog#CHG0113}. The linear range of detection was 2–2000 pg/mL (picograms/milliliter).

Polymerase chain reaction (PCR) for the Mtb genome was performed in five patients (anterior chamber sample in four and vitreous sample in one). PCR was not done in the other five patients as four were already receiving ATT at the time of presentation and one patient had financial constraints. A positive Mantoux test, PCR detecting Mtb genome and findings on CECT chest helped in ruling out sarcoidosis.
Extraction of DNA from Patient Sample

Vitreous and aqueous samples were analyzed for Mtb genome detection. Initial sample handling was conducted in BSL-3 facility and the entire DNA was isolated using MasterPure™ Complete DNA and RNA Purification Kit (Epicentre-Lucigen, Cat No. MC85200). DNA was also isolated from M. tuberculosis, H37Rv strain, culture. The yield and quality (ratio of absorption at 260 and 280 nm) of DNA product was measured using NanoDrop™ One (Thermo Fisher Scientific, ND- ONE-W4).

Detection of M. Tuberculosis DNA Using Real-Time PCR and TaqMan Probes

Two probes were designed (Table 1) for detection of M. tuberculosis gene markers, i.e. MPB 64 (NC_018143; Rv1980c) and IS6110 (X52471). The probes were conjugated with 5'-FAM and 3'-TAMRA. A real-time PCR reaction (20 μL, microliter) was setup using Takyon™ Rox Probe MasterMix dTTP Blue (Eurogenetec, Cat. No. UF-RPMT-B0701), 250 nanometre (nm) probe, 300 nm forward and reverse primers, and 5 μL DNA. The reaction was performed in Mastercycler® ep realplex4 (Eppindorf AG Hamburg, Cat. No. 6302 010760). The following thermal cycling specifications were performed 3 minutes at 95°C and 40 cycles each for 10 seconds at 95°C, 45 seconds at 53°C(Mpb64)/61°C (IS6110), and 30 seconds at 72°C. All reactions were run in duplicate or triplicate form. The DNA was diluted so that 5 μL contained 10²–10⁶ copies. A standard curve was plotted between the copy number and control value from real-time PCR to calculate the bacterial load in patient samples.
Results

A total of 10 eyes of 10 patients were included in the study. Eight patients were females and 2 patients were males. The mean age of presentation was 25.9 ± 12.27 years (5–51 years). There was a past history of pulmonary tuberculosis in 6 out of 10 patients. Left eye was affected in 7 out of 10 patients. Anterior uveitis (SUN classification) was present in 6 patients. Varying grades of vitritis was found in all the patients. Eight patients presented with a choroidal granuloma and two patients with optic nerve head (ONH) granuloma. Multiple patches of choroiditis extending till the equator were noted along with ONH granuloma in one patient. Exudative RD with
### Table 1. Primer and probe design.

<table>
<thead>
<tr>
<th>S. no.</th>
<th>Gene markers</th>
<th>Probe</th>
<th>Primers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MPB64</td>
<td>5'-CCTACACATCACATCAGCCTGC-3'</td>
<td>Forward: 5'-GTGCCAGATTCAAATGTC-3'&lt;br&gt; Reverse: 5'-GGTGATATTCAATTCGTAAG-3'</td>
</tr>
<tr>
<td>2</td>
<td>IS6110</td>
<td>5'-TGTGCTCTTGAGTTCGCA-3'</td>
<td>Forward: 5'-CCTACATGACACACTCA-3'&lt;br&gt; Reverse: 5'-CGTAAACCCGTAGGT-3'</td>
</tr>
</tbody>
</table>

### Table 2. Clinical profile of patients with tubercular granuloma.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Eye</th>
<th>H/o</th>
<th>TB</th>
<th>Anterior segment</th>
<th>Posterior segment</th>
<th>Baseline BCVA</th>
<th>Final BCVA</th>
<th>Mantoux (mm)</th>
<th>CECT Chest</th>
<th>PCR</th>
<th>ATT</th>
<th>Corticosteroid</th>
<th>No of injections</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>F</td>
<td>Left</td>
<td>Yes</td>
<td>No</td>
<td>Quiet</td>
<td>Vitritis, Choroidal granuloma, exudative RD</td>
<td>6/36, N1/2</td>
<td>6/6, N6</td>
<td>16x18</td>
<td>Active Koch's</td>
<td>Not done</td>
<td>Yes</td>
<td>Oral</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>M</td>
<td>Left</td>
<td>No</td>
<td>No</td>
<td>Quiet</td>
<td>Vitritis, Choroidal granuloma</td>
<td>6/36, N2/4</td>
<td>6/6, N6</td>
<td>1x1</td>
<td>Normal study</td>
<td>Not done</td>
<td>Yes</td>
<td>Oral</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>F</td>
<td>Right</td>
<td>No</td>
<td>No</td>
<td>Quiet</td>
<td>Vitritis, Choroidal granuloma</td>
<td>6/9, N6</td>
<td>6/6, N6</td>
<td>2x2</td>
<td>Normal study</td>
<td>Positive, Aqueous sample</td>
<td>Yes</td>
<td>Oral</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>F</td>
<td>Left</td>
<td>No</td>
<td>No</td>
<td>Flare+2, cells+2</td>
<td>Vitritis, ONH granuloma, exudative RD, Chorioretinitis, Peri-vascularitis</td>
<td>HM</td>
<td>6/24, N12</td>
<td>18x2O</td>
<td>Active Koch's</td>
<td>Positive, Aqueous sample</td>
<td>Yes</td>
<td>Topical, Oral</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>51</td>
<td>F</td>
<td>Left</td>
<td>Yes</td>
<td>No</td>
<td>Flare+1, cells+1, KP's</td>
<td>Vitritis, ONH granuloma, exudative RD</td>
<td>3/60, N36</td>
<td>6/18, N18</td>
<td>20x2S</td>
<td>Active Koch's</td>
<td>Positive, Aqueous sample</td>
<td>Yes</td>
<td>Topical, Oral</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>28</td>
<td>F</td>
<td>Right</td>
<td>No</td>
<td>No</td>
<td>Flare+1, cells+1, 160</td>
<td>Ps. Scleritis</td>
<td>HM</td>
<td>HM</td>
<td>32x3S</td>
<td>Normal study</td>
<td>Positive, Vitreous sample</td>
<td>Yes</td>
<td>Topical, Oral</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>17</td>
<td>F</td>
<td>Left</td>
<td>Yes</td>
<td>No</td>
<td>Flare+1, cells+1</td>
<td>Vitritis, Choroidal granuloma, exudative RD</td>
<td>HM</td>
<td>HM</td>
<td>Z2x2Z</td>
<td>Active Koch's</td>
<td>Not done</td>
<td>Yes</td>
<td>Topical, Oral</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>22</td>
<td>F</td>
<td>Left</td>
<td>No</td>
<td>No</td>
<td>Quiet</td>
<td>Vitritis, Choroidal granuloma, exudative RD</td>
<td>6/60, N36</td>
<td>6/18, N12</td>
<td>20x2O</td>
<td>Active Koch's</td>
<td>Not done</td>
<td>Yes</td>
<td>Oral</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>23</td>
<td>F</td>
<td>Left</td>
<td>Yes</td>
<td>No</td>
<td>Flare+2, cells+2</td>
<td>Vitritis, Choroidal granuloma, exudative RD</td>
<td>6/6, N6</td>
<td>6/6, N6</td>
<td>20x2Z</td>
<td>Active Koch's</td>
<td>Not done</td>
<td>Yes</td>
<td>Oral</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>36</td>
<td>M</td>
<td>Right</td>
<td>Yes</td>
<td>No</td>
<td>Flare+2, cells+2</td>
<td>Vitritis, Choroidal granuloma, exudative RD</td>
<td>3/60, N36</td>
<td>28x3O</td>
<td>Active Koch's</td>
<td>Positive, Aqueous sample</td>
<td>Yes</td>
<td>Topical, Oral</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

TB-Tuberculosis, BCVA-Best corrected visual acuity, CECT-Contrast enhanced computed tomography, PCR-Polymerase chain reaction, ATT-Anti-tubercular therapy, O NH-Optic nerve head, RD-Retinal detachment, HM-Hand movements, KP-Keratic precipitates, PSC-Posterior subcapsular cataract, PS-Posterior synechiae, F-Female, M-Male
SRF was found in 8 patients. Eight patients reported a positive Mantoux test. CECT chest was suggestive of active pulmonary TB in seven patients. PCR detected Mtb genome in four aqueous samples and one vitreous sample. Four drug ATT was started in five patients and in the other five patients the ongoing ATT was continued, for a minimum duration of 9 months (9–12 months) (Table 2).

At baseline presentation, 9 patients had best corrected visual acuity (BCVA) <6/36 (snellen’s chart) and one patient with 6/9. At the last follow-up, four patients had BCVA 6/6, two with 6/18 and four patients < 6/24. The mean duration of follow-up was 13.8 ± 7.0 months (9–24). At the last follow-up, complete regression of the granuloma with CRA and resorption of the SRF was seen in all the patients.

Case 1 had a paradoxical worsening after starting ATT and was treated with intravenous methyl prednisolone (IVMP) following which complete regression of the granuloma was seen. Case 7 developed total rhegmatogenous RD for which pars plana vitrectomy with silicone oil injection was performed.

The mean baseline VEGF-A level was 1004.27 ± 411.40 pg/ml (401.32–1688.95). The mean VEGF-A level at the time of last injection was 27.62 ± 46.86 pg/ml (6.9–131.83). A significant decrease in the VEGF-A level was found with successive intravitreal injections. Table 3 shows the correlation of the VEGF-A levels with the clinical response of tubercular granulomas.
Case reports

Case 1

A 24-year-old female presented with diminution of vision in the left eye for last 5 days. She was diagnosed with pulmonary TB and was on ATT for the last 2 months. BCVA in the right eye was 6/6, N6 and in the left eye 6/36, N12. Right eye fundus was within normal limits. Left eye fundus showed a large choroidal granuloma measuring × 6 mm in the superior quadrant with intraretinal hemorrhage and SRF reaching till the macula. The disc was hyperemic with surrounding granuloma and a small 1 × 1 mm choroidal granuloma was noted inferotemporal to the disc (Figure 1). OCT through the macula showed SRF and scan through the superior granuloma showed a choroidal bump with SRF and intraretinal cystic spaces. Mantoux test was positive (16x18mm). CECT chest showed fibro-parenchymal lesion in the left upper lobe and calcified lymph nodes bilaterally suggestive of active Koch’s. ATT was continued and oral corticosteroids (1.5 mg/kg/day) were added. An intravitreal injection of bevacizumab and moxifloxacin was given. Baseline VEGF-A was analyzed as 927.56 pg/ml. At 2-weeks follow up, extensive CRA was seen in the area of previously noted granuloma. However, a new granuloma was seen at the temporal edge of the CRA corresponding to the healed superior granuloma, extending into the macular area and threatening the fovea. This was diagnosed as a paradoxical reaction and treated with IVMP 1 gm/kg for 3 days followed by high dose oral corticosteroids (2 mg/kg/day) along with a repeat intravitreal injection. VEGF-A level was analyzed as 422.16 pg/ml after the first intravitreal injection.
Subsequent follow-up at 2 weeks, BCVA in the left eye improved to 6/6, N6. Fundus showed mild disc hyperemia, complete regression of the granuloma along with CRA and pigmentation and few hard exudates at the macula. OCT showed a normal foveal contour with complete resorption of the fluid.

**Case 2,3**

Case 2 (33 years, male) and case 3 (22 years, female) presented with uniocular diminution of vision. Case 2 had an exposure of pulmonary TB. In both the patients, on fundus examination there was presence of a choroidal granuloma with vitritis along with perivasculitis in case 3. Mantoux test was negative and CECT chest was normal in both the patients. PCR of the aqueous sample was positive for Mtb genome for case 3 and was not done for case 2 due to financial constraints. Both the cases were diagnosed as possible ocular TB. ATT and oral corticosteroids (1 mg/kg/day) were started for both the patients by our in-house physician. Two intravitreal injections of bev-acizumab and moxifloxacin were administered at a weekly interval. Baseline VEGF-A level in case 2 and 3 was 1688.95 pg/ml and 401.32 pg/ml which decreased to 1140.70 pg/ml and 176.74 pg/ml respectively after one intravitreal injection. In case 2, the choroidal granuloma completely melted away and patient gained BCVA of 6/6, N6 (Figure 2). In case 3, the patient gained BCVA of 6/6, N6 and regression of the granuloma was seen with CRA and pigmented scarring and hard exudates at the macula (Figure 3).

**Case 4**

A 5-year-old girl presented with diminution of vision in the left eye for the last 2 months. She gave a history of cough with expectoration. BCVA in the
right eye was 6/6, N6 and left eye was hand movements (HM) close to face. Fundus examination of the left eye showed a large granuloma infiltrating the optic nerve head with multiple patches of choroiditis extending till the equator (Figure 4). Mantoux test was positive (18×20 mm) and CECT of the chest showed bilateral multiple ill-defined centri-lobular nodules with surrounding ground glass opacification and multiple necrotic discrete to conglomerate mediastinal and hilar lymph nodes suggestive of active pulmonary Koch’s. She was started on four drug ATT along with oral corticosteroids (1 mg/ kg/day). PCR was positive for Mtb genome. Four intravitreal injections of bevacizumab and moxifloxacin were administered on a weekly interval. Baseline VEGF-A level was 667.82 pg/ml. It decreased to 376.78 pg/ml, 224.30 pg/ml, and 131.83 pg/ml, respectively, after successive intravitreal injections. The ONH granuloma was found to regress with each injection. Follow-up at 9 months on the completion of ATT, her vision improved to 6/24, N12. Fundus showed mild pallor of the disc with peripapillary CRA and complete regression of the granuloma.

Case 5

A 51-year-old female complained of diminution of vision in both the eyes for the last 3 months. She had a history of pulmonary TB fifteen years back for which she had taken

<table>
<thead>
<tr>
<th>Size/Location</th>
<th>SRF</th>
<th>3×6/peripheral</th>
<th>Regressed</th>
<th>Decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regressed</td>
<td></td>
<td>3×6/peripheral</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>IVMP</td>
<td></td>
<td>3×6/peripheral</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>Size/Location</td>
<td>SRF</td>
<td>CRA</td>
<td>VEGF-A</td>
<td>ATT</td>
</tr>
<tr>
<td>---------------</td>
<td>-----</td>
<td>-----</td>
<td>--------</td>
<td>-----</td>
</tr>
<tr>
<td>4×6/Peripheral+ Posterior</td>
<td>Absent</td>
<td>Absent</td>
<td>927.56</td>
<td>8 weeks</td>
</tr>
<tr>
<td>1×2/Peripheral+ Posterior</td>
<td>Absent</td>
<td>Absent</td>
<td>422.16</td>
<td>9 weeks</td>
</tr>
<tr>
<td>2×3/Peripheral+ posterior</td>
<td>Absent</td>
<td>Absent</td>
<td>12 weeks</td>
<td>Oral steroids</td>
</tr>
</tbody>
</table>

### ATT.

BCVA in the right eye was 6/9, N6 and in the left eye 3/60, N36.
Anterior segment of the right eye showed old keratic precipitates (KP). Left eye showed cells+1, flare+1, mutton fat KP’s, and posterior subcapsular cataract. Fundus of the right eye showed peripapillary CRA with pigmented scarring and the left eye showed a large granuloma infiltrating the ONH with intraretinal hemorrhage and peripapillary serous retinal detachment involving the macula (Figure 5). OCT through the disc confirmed a granuloma with surrounding SRF detaching the macula. Mantoux test was positive (20×25 mm) and CECT chest showed a focal area of subsegmental collapse with pulled up major fissure in the apical-posterior segment of the left upper lobe suggestive of old Koch’s and a small focal area of fibro-parenchymal lesion in the apical segment of the right.

Figure 1.
Case 1:

(a) Left eye fundus photo showing a large choroidal granuloma 3 × 6 mm (red arrow), hyperemic disc with surrounding granuloma (green arrow) and a 1 × 1 mm choroidal granuloma inferotemporal to the disc (yellow arrow). (b) OCT macular scan showing intraretinal cystic spaces (yellow arrow) and subretinal fluid (red arrow). (c) OCT scan through the superior granuloma showing choroidal bump with intraretinal cystic spaces (yellow arrow) and subretinal fluid (red arrow). (d) Fundus photo showing regression of the granuloma (yellow arrow) 2 weeks after the first injection with a new lesion due to paradoxical worsening (red arrow). (e) OCT macular scan showing subretinal fluid (yellow arrow). (f) OCT scan through the new lesion showing choroidal bump (yellow arrow) with subretinal fluid (red arrow). (g) Fundus photo showing completely regressed granuloma (red arrow) with hard exudates at the macula (green arrow) after IVMP and second injection. (h) OCT macular scan showing normal foveal contour (i) OCT scan through the granuloma showing normal choroidal structure.
Figure 2.

Case 2:

(a) Left eye fundus photo showing a $3 \times 6$ mm choroidal granuloma in the superior quadrant (red arrow). (b and c) Fundus photo showing melting of the granuloma after the first and second injections, respectively. (d) Fundus photo showing complete disappearance of the granuloma at 9-month follow-up.
Figure 3.

Case 3:

(a) Right eye fundus photo showing a $3 \times 4$ mm choroidal granuloma along the inferior arcade (red arrow). (b and c) Fundus photo showing regressing granuloma (red arrow) along with hard exudates at the macula (yellow arrow) after the first and second injections, respectively. (d) Fundus photo showing regressed choroidal granuloma (red arrow) at 9-month follow-up.

Figure 4.
Case 4:

(a) Left eye fundus photo showing ONH granuloma (red arrow) with surrounding choroiditis (green arrow) and peri-vasculitis (yellow arrow).

(b–e) Fundus photo showing regression of the granuloma with resolving choroiditis and peri-vasculitis after the first, second, third, and fourth injections, respectively. (f) Fundus photo showing completely regressed ONH granuloma with resolving perivasculitis (yellow arrow) at 3-month follow-up. (g) Fundus photo at 9-month follow-up showing normal ONH contour (red arrow).

Figure 5.

Case 5:

(a) Left eye fundus photo showing an ONH granuloma with intraretinal hemorrhage (yellow arrow). (b) OCT scan through the ONH showing granuloma (yellow arrow) with surrounding subretinal fluid (red arrow). (c) OCT macular scan showing subretinal fluid (yellow arrow). (d) Left eye
fundus photo showing complete regression of the granuloma after three injections. (e) OCT scan showing normal ONH contour. (f) OCT macular scan showing complete resorption of the subretinal fluid.

upper lobe suggestive of active Koch’s. PCR was positive for Mtb genome. She was started on four-drug ATT, oral corticosteroids (1.5 mg/kg/day) and topical prednisolone acetate eye drops (1%) with atropine (1%). Three intravitreal injections of bevacizumab and moxifloxacin were administered at a weekly interval. Baseline VEGF-A level was 787.91 pg/ml which decreased to 272.02 pg/ml and 156.87 pg/ml subsequently after repeat injections. Complete regression of the granuloma with resorption of the SRF was noted. OCT showed a normal contour of the disc and the macula.

Discussion

In our series of consecutive 10 eyes of 10 patients with intraocular tubercular granulomas, in addition to the usual ATT and oral corticosteroids, weekly injections of anti-VEGF bevacizumab and moxifloxacin led to a prompt regression of these granulomas that included eight choroidal and two ONH granulomas. Five of these patients, who had not received prior ATT, in whom aqueous humour was subjected to PCR showed the presence of the Mtb genome in the intraocular fluid, confirming the tubercular etiology of these granulomas.13 We also found very high levels of VEGF-A in the pretreatment aqueous humour. The VEGF-A levels decreased substantially in these eyes following the weekly intravitreal therapy and correlated significantly with the regression of the granulomas. We thus provide evidence for the rational use of the anti-VEGF therapy in the
management of intraocular tubercular granulomas. The monthly use of anti-VEGF therapy currently the gold standard for neovascular age-related macular degeneration (AMD) and macular edema due to diabetic retinopathy and retinal vascular occlusion is based on the presence of VEGF in the aqueous/vitreous humour of these patients. However, we observed much higher VEGF-A levels in tubercular granulomas than have been reported in the aforementioned retinal diseases. Hence, we feel that a much higher frequency of the anti-VEGF therapy was required in our patients. The progressive decrease in the VEGF levels following weekly injections has thus justified this approach.

VEGF is a known biomarker for active TB disease in pulmonary as well as extrapulmonary sites, to monitor disease severity, bacterial burden, and therapeutic responses in pulmonary TB. Matsuyama et al. analyzed the serum VEGF levels (722.6 ± 362.2 pg/ml) in patients with active pulmonary TB and found them significantly higher than in old treated TB patients (185.1+158.4 pg/ml). The highest serum VEGF level was 1300 pg/ml which decreased to <100 pg/ml, 6 months after ATT. They showed that the serum VEGF levels of patients with active pulmonary TB decreased parallel to improvement of the disease.

A vision threatening paradoxical worsening of IOTB due to an immunological reaction is a major fear of starting ATT which requires stepping up of oral corticosteroids and at times needs intravenous corticosteroid therapy. This is well demonstrated by case 1 of our series. However, Jain et al. have reported a case of paradoxical worsening in a HIV-infected patient with tubercular granuloma that did not respond to oral
corticosteroids but showed an excellent response to two injections of bevacizumab. Agarwal et al.7 also reported a case in whom even after 3 months of ATT there was no regression of the granulomas which was associated with an exudative RD. However, three weekly injections of bevacizumab and moxifloxacin led to a complete regression of the granulomas with resolution of the exudative RD.

In the last decade, a few case reports have been published highlighting the use of intravitreal anti-VEGF agents as mono-therapy or as adjunct to ATT and oral corticosteroids for treating tubercular granulomas.7–12 Bansal et al.11 and Babu et al.12 each treated a case of vascularized tubercular granuloma with monthly intravitreal injections of bevacizumab along with ATT and corticosteroids leading to regression of the granuloma and resolution of exudative RD. Bansal et al.11 in their case have also shown a prompt regression of the recurrent granuloma which occurred after one year of stopping ATT and was treated with two bevacizumab injections alone thereby maintaining the remission of the granuloma. Invernizzi et al.10 have reported the first case of an ONH tubercular granuloma with surrounding SRF successfully treated with monthly injections of bevacizumab along with ATT and oral corticosteroids. Jain et al.8 have reported complete regression of a vascularized tubercular granuloma with a single intravitreal injection of ranibizumab without adding ATT as they did not find any evidence of systemic TB. In contrast, we started ATT without any evidence of systemic TB in cases 2 and 3 based on the clinical signs, as suggested by Gupta et al.13

Ocular TB is a form of extrapulmonary TB presenting as uveitis in TB-
endemic countries like India. The classic histopathological finding in IOTB is epithelioid cell granuloma with a central area of caseation necrosis. Datta et al. have shown that in both human and rabbit tubercular granulomas, VEGF is most highly expressed in the inner macrophage layer that surrounds the necrotic core. They also noted that vasculature, with the highest density in the periphery of these granulomas, was both structurally, morphologically, and functionally abnormal. Further they have shown that bevacizumab normalizes the granuloma vasculature, reduces hypoxia, and also enhances the small molecule delivery of anti-TB drugs.

A multidrug therapy regimen of ATT should not logically allow multidrug resistant TB (MDR-TB) to emerge. Yet, it is a well phenomenon in pulmonary TB and other extrapulmonary sites. Moreover, reports of MDR-TB are emerging in ophthalmic literature and posing a major therapeutic challenge that calls for innovative host directed therapies. Of all the drugs that are used to treat TB, isoniazid is the only bactericidal drug which blocks the cell wall synthesis of the dividing Mtb, and its efficacy is determined directly by the rate of the multiplication of Mtb. Also, isoniazid is not effective against non-multiplying or dormant Mtb. Wayna et al. demonstrated that Mtb stops multiplying and goes into dormancy in hypoxic conditions.

It has been proposed that one of the main factors in the emergence of MDR-TB may be the abnormal vessels that do not allow the ATT drugs to diffuse equally in all the parts of the granuloma. This effectively reduces the ATT to a monotherapy thereby enhancing the chances of developing MDR-TB. Using anti-VEGF drugs such as bevacizumab ensures equal distribution of all the therapeutic agents in the granuloma significantly reducing the chances of
The anti-TB drugs were introduced for the treatment of TB without knowing the pharmacokinetics and their differential concentration in various cellular components of the tubercular granuloma. The rationale for using multiple drugs in ATT is due to the action of various drugs on different phases of Mtb.25 Tubercular granulomas show a favorable but slow response when treated with ATT.27 There have been reports of rapid diminution of vision with early onset of intraretinal and subretinal neovascularization due to arteriovenous communication leading to the formation of retinal arterial proliferans (RAP) in these granulomas.28,29 This may lead to a painful blind eye requiring a removal while being on ATT.30

In recent years, use of high-performance liquid chromatography coupled to tandem mass spectrometry in rabbit model of TB has shown that compared to the plasma levels, moxifloxacin is preferentially accumulated in the macrophages with a high intracellular to extracellular ratio compared to other anti-TB drugs like isoniazid, rifampicin, and pyrazinamide.25 However, it diffuses poorly into the necrotic center of the granuloma which can be penetrated only by pyrazinamide. Therefore, we used intravitreal moxifloxacin to target the most active component of the tubercular granuloma, that is activated macrophages harboring Mtb to facilitate a quick elimination of the organisms.

Our case series differs in the following ways from what has been previously reported, firstly we gave a combination of intravitreal anti-VEGF
bevacizumab and moxifloxacin injection in comparison to only anti-VEGF injections used in the past. Secondly, previous case reports gave monthly anti-VEGF injections in the management of tubercular granulomas, whereas we gave weekly injections in all our patients. The rationale for repeating the anti-VEGF injection every week till the regression of the granulomas was the five times higher mean baseline intraocular VEGF-A level-1004.27 ± 411.40 pg/ml (401.32–1688.95) as compared to the mean baseline VEGF-A level-179.7 ± 88.4 pg/ml (74.5–521.6) in patients with neovascular AMD, and that the half-life of intravitreal bevacizumab ranges between 2.5 and 7.3 days in non-vitrectomized eyes that may be further shortened due to the breakdown of the blood retinal barrier secondary to the inflammation leading to early washout of the drugs. Thirdly, we have also correlated the clinical regression in each case with the corresponding decreasing levels of the VEGF-A, which has never been reported earlier.

It is all but intuitive that efforts should be made not only to restore the vision of the patient quickly but also normalize the vasculature of the tubercular granuloma so that the ATT drugs effectively reach the granuloma and regress it besides preventing the emergence of MDR-TB and dormant-TB in the ocular tissues. In view of better understanding of the diffusion of ATT into the granuloma, it may be speculated that purposefully restricting to the conventional treatment with ATT and oral corticosteroids may allow for a slower response and increase the risk of MDR-TB and dormant-TB with a resultant recurrent and difficult to treat granuloma in the eye.

In view of only anecdotal reports in the literature, and absence of any recommended guidelines for the treatment of tubercular granulomas with
anti-VEGF agents, we were driven by our earnest desire to bring about a quick regression of the granulomas and restore the vision of our patients. The question of the most effective frequency of anti-VEGF in these granulomas can only be addressed in multicentric large controlled trials, which given the small numbers is not possible to do in single center studies. Our study is at best the proof of a conceptual clinical study and should prompt a controlled clinical large trial in the near future for formulating new guidelines for the management of these vision threatening tubercular granulomas.

Studies have reported the risk of retinal pigment epithelium (RPE) atrophy on repeated intravitreal anti-VEGF injections but this toxic effect has only been found in eyes with neovascular AMD who receive these injections in perpetuity unlike a limited use in our patients. The development of complete RPE and outer retinal atrophy (CRORA) is, however, inversely related to the number of anti-VEGF injections. We believe there is a much greater risk of macular scarring and RPE and outer retinal atrophy by delaying the regression of these granulomas by using the conventional treatment of ATT and oral corticosteroids.

There is an inherent risk of endophthalmitis with intravitreal injections irrespective of their frequency and thus calls for a meticulous aseptic technique. We followed the standard protocols that are universally recommended and accepted all over the world. However, the risk of infection has not deterred the use of intravitreal injections that are now considered as the most frequent intervention in the entire world of medicine.
In our study, we collected anterior chamber sample for VEGF analysis, though better would have been to collect the vitreous sample that possibly would have shown a much higher VEGF level, as the granuloma is in the posterior segment of the eye. However, this would have required an active intervention in the form of a vitreous biopsy or vitreous aspiration multiple times for which we did not get an ethical clearance.

The limitations of this study are a small cohort, single center study, non-randomized with absence of a control arm, and inability to correlate VEGF levels with findings on FFA or ICGA as they were not performed in all the patients.

Conclusion

Very high levels of VEGF-A are found in patients with intraocular tubercular granulomas. Intravitreal injections of anti-VEGF along with moxifloxacin may be beneficial as an adjunct to ATT and oral corticosteroids for a prompt regression of these tubercular granulomas. More frequent than monthly injections may be required in comparison to patients with neovascular AMD. The formulation of treatment guidelines for tubercular granulomas may require multicentric controlled trials with a larger number of patients in future.

Acknowledgments

Amod Gupta Professor Emeritus Advanced Eye Center
PGIMER, Chandigarh-160012, India Email id: dramodgupta@gmail.com

Disclosure statement
No potential conflict of interest is reported by the author(s).

**Funding**

The author(s) reported there is no funding associated with the work featured in this article.

**ORCID**

Manisha Agarwal, MS, DNB  http://orcid.org/0000-0002-2277-001X

**References**


34. Moisseiev E, Waisbourd M, Ben-Artsi E, et al. Pharmacokinetics...


CHOROIDAL AND RETINAL THICKNESS VARIATIONS IN OCULAR ALBINISM

Introduction:

Albinism is a genetic disease having an autosomal recessive or X-linked inheritance pattern. In albinism, the melanin biosynthesis in melanocytes is affected resulting in absent or reduced melanin pigment. This in turn causes hypopigmentation of the skin, hair and eyes.[1,2] Ocular features in albinism include poor vision, nystagmus, high refractive errors, iris and fundus hypopigmentation, foveal hypoplasia and mis-direction of the optic nerves.[3,4] All individuals with albinism have the above ocular features but the amount of skin, hair and iris pigment can vary depending on the gene and the mutation involved. A broad range of refractive errors have been noted in albinism, ranging from high myopia to high hyperopia. Wildsoet et al studied the refractive errors and its implications in albinism in the context of emmetropisation and found hyperopia to be the most common refractive error in albinotic patients.[5]
The choroid is a highly vascular tissue located between the retina and sclera and plays an active role in the process of emmetropisation by adjusting its thickness and pushing the retina and sclera forward or backward.\cite{6} Growth factors released from the choroid could play a potential role in remodelling the scleral extracellular matrix and thereby contribute to emmetropisation.\cite{6,7} Also, choroidal thickness has been shown to predict the normal ocular growth in chicks and thus can have a significant role in emmetropisation.\cite{8} The enhanced depth imaging – optical coherence tomography (EDI-OCT) image is useful to visualize the structural abnormalities in the choroid and also to measure retinal and choroidal thickness. The absent melanin pigment in the melanocytes in albinism could lead to structural changes in the choroidal layers. Also, a recent publication suggested that the changes in melanin quantity could play a significant role in the choroidal measurements on OCT.\cite{9}

OCT findings in albinism are rarely documented. There is limited information in the literature regarding choroidal changes seen on OCT in albinism. This probably is due to the difficulties encountered in capturing images in albinotic patients due to poor fixation as a result of nystagmus, especially in the younger age group. One study from Turkey by Karabas et al. noted decreased subfoveal choroidal thickness in 10 patients with ocular albinism (OA) compared to age-matched normal healthy children on EDI-OCT imaging.\cite{10} The major limitations in this study were the small sample size and the presence of nystagmus, thereby not allowing high-quality OCT scans to be acquired. Also, the technique for obtaining the choroidal thickness at the fovea was different where they considered the average of
the choroidal thickness measurement values obtained at 4000 µm, 4500µm and 5000µm from the optic disc. The incorporation of eye tracking software in the newer generation OCT machines helps to reduce the motion artefacts and may enable better centration of the scans on the expected fovea in albinism. In another study, Healey et al on OCT noted that in the presence of albinism, there was increased association of severe foveal hypoplasia with high hyperopia and poor visual acuity. They concluded that the failure of emmetropisation was not attributable to the presence of foveal hypoplasia.\[11\] Another study by Pillay et al noted higher central foveal thickness but thinner retinal thickness measurements in the parafoveal and perifoveal regions.\[12\]

With this limited literature, the authors planned to study the retinal and choroidal thickness variations in albinotic patients and compared them with age, sex and axial length matched healthy control subjects.

**Methods:**

In this retrospective study, clinical and imaging findings were compared between the eyes with albinism and age, sex and axial length matched control subjects at the department of Retina, in South India. The study protocol was approved by the institutional review board (C/20/10/010) and the research followed the tenets of the Declaration of Helsinki. All patients provided informed consent for participation before being included in the study.

**Selection of cases:**

A diagnosis of OA was based on the presence of the following clinical
features: presence of nystagmus and photophobia, iris transillumination, reduced fundus and/or skin and hair pigmentation, foveal hypoplasia with absent foveal reflex and reduced visual acuity.\[13,14\] All patients underwent a detailed ophthalmic examination including measurement of Snellen best-corrected visual acuity (BCVA), cycloplegic refraction with cyclopentolate 1% eye drops for patients with age < 20 years or with tropicamide 1% eyedrops for older patients and those having high refractive error or poor visual acuity, slit-lamp examination, non-contact tonometry (Topcon CT-80, Oakland, NJ, USA) and dilated fundus examination with either cyclopentolate 1% or tropicamide 1% eye drops. Axial length (AL) measurement was done using optical low-coherence reflectometry (Lenstar 900; Haag-Streit Diagnostics, Koeniz, Switzerland). Fundus findings were documented with ultrawide image colour fundus photographs using the Optos, Daytona (Marlborough, MA, USA) machine. Macular retinal and choroidal layer thicknesses were measured using spectral domain-OCT (Heidelberg Spectralis, Germany).

**Selection of controls:**

The control group was selected from a cohort of patients having an anatomically normal fundus appearance. They were matched with the study group for age, gender and axial length. The number of controls selected were in the ratio of 1:1 for the cases.

**Retinal imaging using spectral domain-OCT:**

On OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany), the macular retinal and choroidal layer thicknesses were measured. All OCT
scans were performed by the same experienced operator during the morning hours from 9 a.m. to 12 p.m. A single-line horizontal raster scan using the EDI mode extending from the temporal margin of the optic nerve head and passing through the foveal centre (either the actual fovea or expected foveal location when there was no visible pit identified with the help of the adjacent infrared image) was performed with 15 frames averaged to improve the image quality. OCT scans were obtained while the patient focused on the fixation target in their habitual head posture as this would allow for the null point of the nystagmus and their preferred retinal locus of fixation. The scan with no motion artefacts, higher signal to noise ratio with instrument quality score ≥ 20 dB was selected for further analysis. All thickness measurements were made on the OCT using the automated layer segmentation tool in the proprietary machine software. The retinal thickness was measured in an automated fashion from the internal limiting membrane to the outer border of the retinal pigment epithelium at the assumed fovea. The protocol for measuring the choroidal thickness was similar to that followed by Regatieri et al.\textsuperscript{[15]} For measuring the choroidal thickness, the outer choroid-sclera junction was identified, cross-checked, marked and measured by one of the authors in the study (SA). The choroidal thickness was measured manually from the outer border of the retinal pigment epithelium to the inner border of the sclera (Figure 1). The choroidal thickness was measured at the fovea and at intervals of 500µm from the fovea and extending till 2000µm of the scan nasally and temporally. The retinal thickness and choroidal thickness were measured at each of these points using the 1:1-pixel protocol.
Statistical Analysis:

All data were analysed with GraphPad Prism software (version 9.0.0 [121]) for Windows, San Diego, CA. Normal distribution of quantitative variables was checked using the D’Agostino & Pearson omnibus normality test. Refraction data were converted to spherical equivalent, which was calculated as the spherical dioptric power plus one-half of the cylindrical dioptric power. BCVA was recorded in Snellen units and was converted to logarithm of the minimum angle of resolution (logMAR) for statistical analyses. Snellen equivalents of logMAR vision were recalculated for documenting in the tables. For non-parametric quantitative data, Mann-Whitney U test was used for analysis between the 2 groups. A generalised estimating equation model for both eyes was used for estimating the average response over the population to compensate for both eyes’ inclusion of subjects. A p value <0.05 was considered statistically significant.

Results:

This study included 48 eyes of 24 cases with OA and 48 eyes of 24 control subjects for evaluation. Skin hypopigmentation and hair hypopigmentation was noted in 20 (83%) and 18 (75%) patients respectively. There were 15 males and 9 females in each group. The mean age was 28.3 ± 11.6 years (range: 5-46 years) in the patients with OA and 29.9 ± 10.6 years (range: 7-48 years) in the normal control group. All the cases had spherical equivalents ranging from -8.5D to +10.5D while in the control group, the spherical equivalent ranged from -8.0D to +10.0D. The mean axial length in the cases group was 26.65 ± 4.32mm and in the control group was 25.98 ± 5.11mm.
respectively. Mean best-corrected visual acuity in OA group was 0.655 ± 0.382 (Snellen equivalent - 20/90) and for the control subjects, it was 0.058 ± 0.152 (Snellen equivalent - 20/23). On examination, all cases showed iris transillumination, nystagmus and photophobia while none of the patients in the control group observed these features. Foveal light reflex was absent and the choroidal vessels were prominent due to the absence of pigmentation in all of the patients with OA. Fundus examination was normal in the control group.

The mean retinal thickness in the OA group was 272 ± 34.3µm and in the control eyes was 213 ± 13.8µm respectively. The retinal thickness in the OA group was significantly thicker than in the control group (p<0.001). The choroid was significantly thinner (p<0.001) in the OA cases group compared to the control group at the fovea and at every point measured nasally and temporally. The mean subfoveal choroidal thickness in the OA cases group was 184 ± 78.4µm and in the control group was 287 ± 46.4 µm. The comparison of choroidal thickness between 2 groups at every 500µm of the scan, nasally and temporally is mentioned in ‘Table 1’. We noted that the choroidal thickness was thickest at the presumed fovea and progressively reduced from the fovea towards the nasal and temporal sides of the OCT scan in both groups. No significant difference was noted in comparing the choroidal thickness on the nasal and temporal parts of the scan. Comparisons between the choroidal thickness on the nasal and temporal sides of the scan in both groups is mentioned in ‘Table 2’.

Discussion:
Earlier studies on OA have shown that the choroid might play an important role in the process of emmetropisation in albinotic eyes.\cite{6,7} The deficiency of melanin pigment in the choroidal melanocytes can lead to choroidal anatomical and vascular abnormalities.\cite{9} Before the availability of the EDI-OCT or swept-source technology, there were no other methods available for high-resolution visualisation of the choroid. The findings of this retrospective EDI-OCT study on albinotic patients suggest that patients with OA have a wide range of refractive errors and also have an increased retinal and reduced choroidal thickness compared to the age, sex and refractive error matched healthy controls. There was no significant difference in the choroidal thickness on the nasal and temporal sides of the macula, unlike healthy controls as seen in our study and literature.

These findings are agreeable to those reported by Karabas et al,\cite{10} where the subfoveal and peripapillary choroidal thickness was lesser than the normal control subjects. In their study, the subfoveal (measured as an average of values obtained at 4000 µm, 4500µm and 5000µm from the optic disc) and peripapillary choroidal thickness was measured using enhanced depth imaging-OCT scans in a pediatric population in Turkey. Here, cases diagnosed with OA in the Indian population of varying age groups were included and the subfoveal retinal thickness and choroidal thicknesses were measured along the entire horizontal scan length at 500µm intervals from the fovea on either side. In albinism, there is diffuse deficiency of the melanin pigment across the entire fundus. Thus, it would be more meaningful to measure the choroidal thickness across the entire length of the scan rather than measuring just at the subfoveal location especially when the
identification of the exact foveal location is difficult due to foveal hypoplasia. One of the limitations reported in the study by Karabas et al was the difficulty in capturing good quality scans due to poorer vision (20/154) and fixation in pediatric population with nystagmus.[10] Older albinotic patients with better visual acuity (20/90) were a part of this study. Thus, allowing better quality OCT scans to be acquired for measuring the retinal and choroidal thickness. A recent study by Pillay et al measured the retinal thickness at the fovea, perifoveal and parafoveal regions in albinotic eyes.[12] They noted that the retina was thickest at the fovea and progressively became thinner in the perifoveal and parafoveal regions.

A number of factors such as age, axial length, refractive error and race can affect the choroidal thickness measurements.[16–18] In this study, the control subjects were matched with the cases for age, sex and axial lengths. Thus, it is unlikely that the wide range of refractive errors in our cases could have contributed to the significant difference in the choroidal thickness between the case and control groups. Our results represent a true difference between OA and control group in regards to retinal and choroidal measurements.

Also, in this study, the mean choroidal thickness measurement in the healthy control group was slightly lower than the initial descriptive study of choroidal structure in the normal population done by Arora et al.[16] In this study, the choroidal thickness at the fovea measured in normal healthy subjects was 287 ± 46.4µm compared to the subfoveal choroidal thickness measured in their study (301.80 ± 46.6µm). This difference occurred mainly due to different instruments used for measuring the choroidal thickness. The
comparisons are only meaningful when performed with the same instrument using the same imaging protocol.[16]

Another important probable theory responsible for the significant thinning of the choroid in albinotic patients could be based on the quantity of the melanin pigment present in the melanocytes of the iris, retinal pigment epithelium and choroid and on the absorption properties of melanin to high wavelength light. The absorption spectrum of melanin is maximum for the visible light (short wavelength) while long wavelength (infrared spectrum) have the least absorption.[19,20] This would mean that in the absence of melanin pigment, the 870 nm wavelength light of Spectralis OCT machine would pass easily through the choroid and allow visualisation of the outer choroid-sclera junction. Based on this theory, a recent paper from our group explained an apparent increase in choroidal thickness in the depigmented areas of the fundus in a patient with choroidal melanocytosis.[9,21] Thereby, one would expect the choroid to be thicker in the albinotic patients as well. However, our study showed contrary results where the choroid was significantly thinner than the control group. The basic difference between the two scenarios is the presence of melanocytes in the albinotic cases and the absence of melanocytes in the depigmented areas of choroidal melanocytosis cases. Also, the retinal pigment epithelium melanin is unaffected in the choroidal melanocytosis cases while it gets affected in the albinotic cases. All these reasons could contribute to the thinner choroid in the albinotic case group.

Literature search didn’t reveal any previous studies that have measured the retinal thickness in OA patients. This could be due to the difficulty in
accurately identifying the fovea on the OCT scan due to nystagmus. In this study, we selected OCT line scan passing through the fovea after identifying it based on the adjacent infrared image. The retinal thickness measured across the scan at the presumed fovea was higher in the OA group compared to the normal control subjects. This could be due to the loss of the foveal pit and presence of the inner retinal layers at the fovea in eyes with OA.

This study has a number of strengths and few limitations as well. One of the major strengths is the relatively large number of cases compared to previously reported studies.[10] Also, cases of all age groups were included, the study did not limit measurements only to the subfoveal location, but measured the choroidal thickness along the entire length of the scan. The methodology used in the current study overcomes the limitations described by Karabas et al.[10] The major limitation of this study was that the changes on the basis of albinism subtype could be not evaluated as genetic testing was not performed for these patients. Secondly, the presence of nystagmus in patients resulted in poor quality scans, and this led to further reduction in total number of cases. Thirdly, we neither did foveal hypoplasia grading nor measured the thickness of the individual retinal layers on OCT scan. Finally, we couldn't do other choroidal biomarkers like choroidal vascularity index due to the average quality OCT scans.

**Conclusions:**

This study demonstrated that in patients with OA, obtaining high quality OCT scans is difficult. The retina at fovea was thicker while the choroid largely in OA cases was thinner compared to normal healthy controls. Solely
based on the analysis of this data on EDI-OCT, it may be implied that the choroidal structural change is related to failure of emmetropisation in these patients. In future, more studies are required to evaluate the role of choroidal metabolism and its relationship to emmetropisation in albinism.

References:


15. Regatieri CV, Branchini L, Fujimoto JG, Duker JS. Choroidal imaging


Table 1: Demographic, refractive error, visual acuity, retinal and choroidal
thickness changes between the ocular albinism group and control group:

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>28.3 ± 11.6</td>
<td>29.9 ± 10.6</td>
<td>0.665</td>
</tr>
<tr>
<td>Sex (M: F)</td>
<td>15:9</td>
<td>15:9</td>
<td></td>
</tr>
<tr>
<td>SE</td>
<td>0.565 ± 4.25</td>
<td>-1.32 ± 4.70</td>
<td>0.712</td>
</tr>
<tr>
<td>VA (logMAR)</td>
<td>0.655 ± 0.382</td>
<td>0.058 ± 0.152</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AXL (mm)</td>
<td>26.65 ± 4.32</td>
<td>25.98 ± 5.11</td>
<td>0.652</td>
</tr>
<tr>
<td>Mean RT</td>
<td>272 ± 34.3</td>
<td>213 ± 13.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SFCT</td>
<td>184 ± 78.4</td>
<td>287 ± 46.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nasal 500</td>
<td>172 ± 74.6</td>
<td>256 ± 47.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nasal 1000</td>
<td>157 ± 63.4</td>
<td>229 ± 39.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nasal 1500</td>
<td>145 ± 59.8</td>
<td>207 ± 33.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nasal 2000</td>
<td>132 ± 56.3</td>
<td>187 ± 39.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Temporal 500</td>
<td>168 ± 68.3</td>
<td>255 ± 42.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Temporal 1000</td>
<td>165 ± 65.2</td>
<td>230 ± 41.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Temporal 1500</td>
<td>160 ± 64.3</td>
<td>223 ± 46.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Temporal 2000</td>
<td>147 ± 57.0</td>
<td>206 ± 54.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: SE – spherical equivalent; VA – visual acuity; AXL – axial length, RT – retinal thickness; CT – choroidal thickness. P value <.05 was considered statistically significant.

**Table 2: Comparison of choroidal thickness between the nasal and temporal sides of the scan in both groups:**

<table>
<thead>
<tr>
<th>Distance from fovea</th>
<th>Cases</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal</td>
<td>Temporal</td>
<td>P value</td>
<td>Nasal</td>
</tr>
</tbody>
</table>

446
<table>
<thead>
<tr>
<th>Distance (μm)</th>
<th>Layer 1 (μm)</th>
<th>Layer 2 (μm)</th>
<th>Layer 3 (μm)</th>
<th>Layer 4 (μm)</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>500μm</td>
<td>172 ± 74.6</td>
<td>168 ± 68.3</td>
<td>256 ± 47.2</td>
<td>255 ± 42.1</td>
<td>0.951</td>
</tr>
<tr>
<td>1000μm</td>
<td>157 ± 63.4</td>
<td>165 ± 65.2</td>
<td>229 ± 39.8</td>
<td>230 ± 41.1</td>
<td>0.932</td>
</tr>
<tr>
<td>1500μm</td>
<td>145 ± 59.8</td>
<td>160 ± 64.3</td>
<td>207 ± 33.9</td>
<td>223 ± 46.5</td>
<td>0.213</td>
</tr>
<tr>
<td>2000μm</td>
<td>132 ± 56.3</td>
<td>147 ± 57.0</td>
<td>187 ± 39.5</td>
<td>206 ± 54.0</td>
<td>0.252</td>
</tr>
</tbody>
</table>

**Figure Legends:**

**Figure 1:**

Single-line horizontal enhanced depth imaging optical coherence tomography (EDI-OCT) scan in a patient with ocular albinism (OA):

This is the EDI-OCT scan of the right eye of a 19-year-old male patient (spherical equivalent = -3D and axial length – 22.1mm) diagnosed with ocular albinism and nystagmus. Here, we also observe the absence of the foveal pit in the scan. (A) This is a representative OCT image measuring the retinal thickness at the presumed fovea. (B) This is a representative EDI-OCT image showing the manual marking of the choroid-sclera junction for measuring the choroidal thickness. (C) This is a representative OCT image measuring the choroidal thickness at the fovea and at 500μm intervals from the fovea and extending till 2000μm nasally and temporally.
SAFETY AND EFFICACY OF SUPRACHOROIDAL TRIAMCINOLONE FOR PSUEDOPHAKIC CME

Abstract

Psuedophakic cystoid macular oedema (PCME) mostly responds to topical steroids and NSAIDs, however intravitreal injections may be required for nonresponsive cases. Suprachoroidal injection of preservative free triamcinolone acetonide (SCTA) is a recent addition to for treatment of cystoid macular edema of uveitis and diabetic retinopathy. We studied safety and efficacy of SCTA in pseudophakic CME.

Methods:

20 patients with PCME unresponsive to topical medication were enrolled. Patients with other macular pathology due to other causes were excluded. The drug was administered with a novel- 26-G needle with intracath sleeve in the OR. Change in BCVA, macular thickness and complications, if any at 6 months were primary outcome measures.
Results:

The baseline visual acuity was logMAR 0.525 which improved to log MAR 0.06 at 1 month (p<0.00) The baseline CME reduced from 451 micron to 261 micron at 2 months (p<0.00). No significant complications like raised IOP, RD or uveitis were noted.

Conclusion:

This modified method of SCTA injection is cost effective and safe for treatment of PCME. This technique may be concurrently used with cataract surgery in patients with high risk for developing macular edema like diabetic retinopathy or uveitic cataracts.

Key words:

Macular edema, Suprachoroidal steroids, Triamcinolone, Cataract surgery complications,

Introduction

Patient expectations have increased multifold after cataract surgery due to the advances in surgeon skills, operating machines and premium intraocular lenses. The modern-day cataract surgery has become like a refractive surgery. Pseudophakic cystoid macular edema (PCME) is a common cause of reduced vision, after cataract surgery, and the incidence may vary from 0.5 - 2.4%. The incidence of PCME is more in patients with diabetes and uveitis. The cost of treatment of CME adds on to the financial burden and is more significant in economically underprivileged population. The patients who develop PCME end up paying more for medical expenses.
pathological cause of macular edema is multifactorial, nevertheless inflammation plays a key role. Topical steroids and nonsteroidal anti-inflammatory (NSAID) drops are the mainstays of therapy for the initial postoperative period; however, chronic PCME requires periocular or intravitreal injections which might cause significant side effects like endophthalmitis, retinal detachment, cataract and glaucoma.[3] Steroid implants, are sustained released drug-eluting devices, which have recently become popular. Although steroid implants are costly, they have fewer side effects like glaucoma and longer duration of action.

Recent studies on outcomes of depot steroid injection of triamcinolone into suprachoroidal space have shown promising results in terms of improved efficacy, reduced side effects and longer duration of action in patients with macular edema due to uveitis and retinal vein occlusion.[4-6] The microneedle used for injection is short and does not enter the vitreous cavity, which might reduce the chances of damage to ocular tissues. Although, the procedure can be performed in an office setting under sterile precautions, the critical limitation is the high cost and non-availability of the specialized microneedle.

Recently innovative technique of delivery of SCTA using intracath and 26 G needle has been reported which seems quite practical and feasible. The superior efficacy of SCTA could be attributed to relative posterior diffusion of the drug and sustained therapeutic levels in the vitreous cavity. The current study was undertaken to study the safety and efficacy of SCTA delivered with such modified technique in patients with PCME after cataract surgery who failed to respond to topical drops.
Methods

Institutional ethical committee clearance was taken for the study from the institution. Patients with chronic PCME (PCME persisting despite of three months of topical NSAIDs- 1% Nepafenac drops, Alcon India) with macular thickness > 300 micron on optical coherence tomography (OCT) were enrolled after informed consent. Patients with hypersensitivity to TA, immune deficiency, glaucoma, uveitis, diabetic retinopathy, and other retinal vascular diseases were excluded.

The comprehensive ophthalmological examination including visual acuity, slit lamp biomicroscopy detailed retina evaluation and optical coherence tomography (OCT) was done as per the study protocol.

Preparation of the Injection

The outer sheath of a 22 G intracath (25 mm length X 0.9 mm outer diameter (Anina India)) was cut into two equal halves and 26 G needle (length 13 mm) was passed through the lumen. Final measurement was taken with calipers and care was taken to expose only the terminal 1- mm bevelled end of the 26 G needle. Preservative free Triamcinolone 4mg/.01 ml (Auro Lab India) was taken in a 1 CC syringe and the 26G needle was connected to the syringe.

One intracath sheath (length of 12 mm) has adequate length to make two separate injections. (Fig 1 A)

The periocular area was cleaned and draped after instilling Proparacaine drops and Betadine 5% with a contact period of 5 minutes. Lid speculum was applied, and patient was asked to look in temporal direction exposing the
superonasal quadrant. A point was marked 4 mm from limbus and the sclera was pierced keeping the needle perpendicular and the beveled tip pointing away from the limbus. Gentle pressure was applied to create dimple on the sclera and the drug was injected gently.

The needle tip was withdrawn and cotton tip or sponge was used to avoid backflow of the drug. Any procedure related complications were documented. Patients were followed up on day 1, 7, 30 and 90 after the injection. At every follow-up visit visual acuity, intraocular pressure, central macular thickness (CMT) and complications if any, were documented.

(Fig 1 B)

**Results**

This study included 20 patients with chronic PCME despite of topical NSAID drops for three months. All the patients had undergone uncomplicated cataract surgery with single piece intraocular lens in the bag implantation using phacoemulsification.

Out of twenty patients 12 (60%) were males and 8 (40%) were females. The mean age of the patients was 54.35 years (SD 7.7 years). The mean duration of treatment of PCME with topical NSAID was 13.75 weeks (SD 1.25) with a range of 12 – 16 weeks.

The table 1 depicts demographic and clinical data of 20 patients who received 0.1 mg Triamcinolone through the suprachoroidal route for psuedophakic CME.

The mean baseline best corrected visual acuity in this series of twenty
patients was 0.52 log MAR (Snellen equivalent 6/24) which improved to 0.06 log MAR (Snellen equivalent 6/6) at the end of four weeks (p<0.005). The central macular thickness reduced from a mean of 451.90 microns at baseline to 261 microns (p<0.005). The intraocular pressure at the baseline was 13.30 mmHg which remained within normal limits at 13.50 mmHg(p=0.64). No significant side effects like uveitis, endophthalmitis, retinal detachment or glaucoma were noted however 2 patients complained of moderate eye pain which subsided with NSAID tablets. Five patients had localized subconjunctival haemorrhage which resolved within one week. At the end of three months, the visual acuity was maintained.

Discussion

PCME is an important complication after the cataract surgery and it is managed using topical NSAIDs, along with steroids; however, intravitreal anti-VEGF or steroid injections may be required for cases not responding to topical drops. The alternative treatment is the use of intravitreal steroid implants due to less effect on IOP, nonetheless the cost is astronomically high and other complications like retinal detachment and endophthalmitis are reported. Quest for finding newer ocular drug formulations and delivery routes have led to description of newer techniques. A recent phase 3 trial on uveitis has demonstrated the efficacy of supra choroidal triamcinolone SCT in macular edema due to retinal vein occlusion & uveitis.[4,6,7]

In preliminary studies, SCT was found to reach a high concentration in the posterior segment with lesser side effects like glaucoma and cataract. The therapeutic level of the drug in the posterior segment was reported to be ten
times higher than the anterior segment.\[^5\] SCT is localised in the suprachoroidal space, at the site of pathology and the local concentration remains high, which improves efficacy and prolongs the duration of action due to depot formulation.

Currently, the limitation for the broader applicability of SCT is non-availability of an appropriate needle for safe injection procedure. In this study we used a low-cost alternative injection system which was easily available & designed from inexpensive sterile material available in the operating room. Use of one intracath to prepare two injections made the procedure further economical. The outer sheath of intracath acts as a guard to the sharp end of the needle which pierces the sclera and remains in suprachoroidal space. The SCT localizes in the suprachoroidal space, which is a potential space and opens while injecting the drug. In cadaver experiments the capacity of suprachoroidal space was found to be 1 ml so the smaller volume of 0.1 ml injected in various clinical studies should not be a cause of concern.

While injecting the drug it should be ensured that terminal 1 mm of the needle tip should be exposed otherwise if the bevelled end is also covered the drug might leak from the gap between the intracath and needle. Another important step is to apply gentle pressure after the sclera is pierced to create a dimple to ensure adequate penetration of the needle so that the drug is injected into the suprachoroidal space.

(Fig 1 B) The bevel of the needle should be pointing away from limbus so that the drug diffuses posteriorly.
The SCTA is practically extraocular procedure like the posterior sub-tenon triamcinolone injection, but direct visualization of the needle makes SCTA safer and more predictable. In addition, since the vitreous cavity is not entered, the chances of sight threatening complications like endophthalmitis, retinal tear, retinal detachment, lens injury are fewer.

Two patients reported moderate eye pain immediately after the procedure, which subsided after one hour with NSAID tablets. The expansion of suprachoroidal space with SCT could be the cause of the pain. Mild conjunctival congestion at the site of injection was noted in 5 patients, which resolved within one week.

SCTA has sustained therapeutic effect as the drug is a depot formulation as supported by pharmacokinetic studies. SCTA may aid in stabilizing the vision in the long-term. As the frequency of the injections required would be less, it would also drastically cut down on the cost of repeated injections. Compared to expensive alternatives, the SCTA injected with this innovative technique would benefit the patients from economically-weaker sections of the society.

The patients in this study had normal IOP at baseline which remained within the normal range at the end of the study. None of the patients required to use of any anti-glaucoma medication. Due care should be exercised while using SCTA in patients with glaucoma and frequent IOP checks should be done in the follow-up period. The efficacy of SCTA has been well established in randomized trials conducted in patients with CME following uveitis. We also excluded patients with other causes of macular edema like patients with
diabetes and uveitis, which may not be practical in a real-world scenario.

The results of current study are encouraging in terms of safety and efficacy of SCTA in pseudophakic CME. The use of innovative technique for injection procedure makes the procedure economical as well as affordable and has potential to become an attractive option in macular edema of varied etiology. Larger randomized controlled trials might be undertaken to further establish the safety and efficacy of SCTA.

Authors do not have any financial disclosures to make, the study was not funded by any grants.

**Figure Legends**

Fig 1 A The outer sheath of intracath is cut and used to cover the 26-gauge needle till the bevelled edge 1 B Optical coherence tomography showing TA deposited in suprachoroidal space (Upper pane) and completely resolved CME (Lower pane)

**References**


Table 1 Demographic and clinical data

<table>
<thead>
<tr>
<th>SEX</th>
<th>AGE</th>
<th>NSAID</th>
<th>BCVA PRE</th>
<th>BCVA POST</th>
<th>CMT PRE</th>
<th>CMT POST</th>
<th>IOP PRE</th>
<th>IOP POST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>55</td>
<td>14</td>
<td>0.6</td>
<td>0</td>
<td>473</td>
<td>287</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>Age</td>
<td>%</td>
<td>Rate</td>
<td>Value 1</td>
<td>Value 2</td>
<td>Value 3</td>
<td>Value 4</td>
</tr>
<tr>
<td>----</td>
<td>-----</td>
<td>-----</td>
<td>---</td>
<td>------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Male</td>
<td>54</td>
<td>12</td>
<td>0.5</td>
<td>0</td>
<td>544</td>
<td>210</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Female</td>
<td>67</td>
<td>14</td>
<td>0.4</td>
<td>0.1</td>
<td>345</td>
<td>270</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Male</td>
<td>46</td>
<td>15</td>
<td>0.6</td>
<td>0</td>
<td>447</td>
<td>269</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Female</td>
<td>43</td>
<td>16</td>
<td>0.5</td>
<td>0</td>
<td>437</td>
<td>266</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Female</td>
<td>43</td>
<td>12</td>
<td>0.6</td>
<td>0.1</td>
<td>332</td>
<td>259</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Male</td>
<td>55</td>
<td>13</td>
<td>0.5</td>
<td>0.2</td>
<td>433</td>
<td>271</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Female</td>
<td>58</td>
<td>15</td>
<td>0.4</td>
<td>0.1</td>
<td>346</td>
<td>258</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Male</td>
<td>62</td>
<td>14</td>
<td>0.5</td>
<td>0.2</td>
<td>632</td>
<td>267</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Male</td>
<td>64</td>
<td>13</td>
<td>0.6</td>
<td>0</td>
<td>542</td>
<td>242</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Male</td>
<td>55</td>
<td>14</td>
<td>0.6</td>
<td>0</td>
<td>456</td>
<td>287</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Male</td>
<td>54</td>
<td>12</td>
<td>0.5</td>
<td>0</td>
<td>544</td>
<td>250</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Female</td>
<td>66</td>
<td>14</td>
<td>0.5</td>
<td>0.1</td>
<td>345</td>
<td>250</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Male</td>
<td>46</td>
<td>14</td>
<td>0.6</td>
<td>0</td>
<td>447</td>
<td>269</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Female</td>
<td>43</td>
<td>16</td>
<td>0.5</td>
<td>0</td>
<td>437</td>
<td>266</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Female</td>
<td>45</td>
<td>12</td>
<td>0.6</td>
<td>0.1</td>
<td>336</td>
<td>259</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Male</td>
<td>55</td>
<td>13</td>
<td>0.5</td>
<td>0.2</td>
<td>432</td>
<td>273</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Female</td>
<td>58</td>
<td>15</td>
<td>0.4</td>
<td>0</td>
<td>346</td>
<td>258</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Male</td>
<td>62</td>
<td>14</td>
<td>0.5</td>
<td>0.1</td>
<td>632</td>
<td>267</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Male</td>
<td>56</td>
<td>13</td>
<td>0.6</td>
<td>0</td>
<td>532</td>
<td>242</td>
<td>12</td>
<td>14</td>
</tr>
</tbody>
</table>
Fig 1 A The outer sheath of intracath is cut and used to cover the 26-gauge needle till the bevelled edge 1 B Optical coherence tomography showing TA deposited in suprachoroidal space (Upper pane) and completely resolved CME (Lower pane)
This paper was judged as the BEST PAPER of Vitreo Retinal Diseases – III Session

**Manisha Agarwal, MS, DNB**

Vitreoretina Department, Dr Shroff’s Charity Eye Hospital, New Delhi, India

**DEHLI OPTHALMOLOGICAL SOCIETY : INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR AND MOXIFLOXACIN THERAPY FOR PROMPT REGRESSION OF INTRAOCULAR TUBERCULAR GRANULOMAS**
Adjunctive Intravitreal Anti-vascular Endothelial Growth Factor and Moxifloxacin Therapy in Management of Intraocular Tubercular Granulomas

Manisha Agarwal, Chanda Gupta, K Varsha Mohan, Pramod K Upadhyay, Aditi Dhawan & Vivek Jha

To cite this article: Manisha Agarwal, Chanda Gupta, K Varsha Mohan, Pramod K Upadhyay, Aditi Dhawan & Vivek Jha (2021). Adjunctive Intravitreal Anti-vascular Endothelial Growth Factor and Moxifloxacin Therapy in Management of Intraocular Tubercular Granulomas, Ocular Immunology and Inflammation. DOI: 10.1080/09273948.2021.2002367

To link to this article: https://doi.org/10.1080/09273948.2021.2002367

Published online: 17 Dec 2021.

Article views: 131

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at https://www.tandfonline.com/action/journalInformation?journalCode=oiio20
Adjunctive Intravitreal Anti-vascular Endothelial Growth Factor and Moxifloxacin Therapy in Management of Intraocular Tubercular Granulomas

Manisha Agarwal, MS, DNB; Chandra Gupta, DNB; K Varsha Mohan, MSc, PhD; Pramod K Upadhyay, MSc, PhD; Aditi Dhawan, BSc, MSc; and Vivek Jha, MD

*Vitreoretina Department, Dr Shroff’s Charity Eye Hospital, New Delhi, India; Product Development Cell, National Institute of Immunology, New Delhi, India

**ABSTRACT

**Purpose:** To report pre and post treatment levels of VEGF-A in the aqueous humour of patients with intraocular tubercular granulomas and study the effect of a combined intravitreal anti-VEGF bevacizumab and moxifloxacin therapy on their regression.

**Methods:** Aqueous samples of 10 consecutive patients with intraocular tubercular granulomas obtained before and after initiating treatment were subjected to ELISA for analyzing intraocular VEGF-A levels. Intravitreal injections of bevacizumab and moxifloxacin were given weekly till complete regression of these granulomas. All patients received the usual four-drug ATT and oral corticosteroids.

**Results:** Mean baseline VEGF-A level was 1004.27±111.40 pg/ml (401.32-1668.35) that reduced significantly to 27.62±46.80 pg/ml (6.9-131.83) at the last injection. Mean number of intravitreal injections was 3.1 (2-4). We found significant correlation of decreasing levels of aqueous VEGF-A with the clinical regression of these tubercular granulomas.

**Conclusions:** Intraoccural T 8 granulomas have high levels of VEGF-A. Weekly intravitreal injections of anti-VEGF bevacizumab with moxifloxacin as an adjunct to the standard care may cause prompt regression of tubercular granulomas.

**Abbreviations:** TB: Tuberculosis; IOTB: Intraocular tuberculosis; VEGF: Vascular endothelial growth factor; ATT: Anti tuberculosis therapy; AMD: Age-related macular degeneration; SRF: Subretinal fluid; ELISA: Enzyme immunoassay; PCR: Polymerase chain reaction; ODH: Optic nerve head; MDR-TB: Multidrug-resistant tuberculosis; pg/ml: picogram/milliliter; RSR: Erythrocyte sedimentation rate; CECT: Contrast enhanced computed tomography; DNA: Deoxyribonucleic acid; RNA: Ribonucleic acid; BSL: Biosafety level; BVA: Best corrected visual acuity; HA: Hand movements; KP: Keratic precipitates; PSC: Posterior subcapsular cataract; PS: Posterior synechiae; CDA: Chorioretinal atrophy; IWM: Intravenous methyl prednisolone; OCT: Optical coherence tomography; RPE: Retinal pigment epithelium; FFA: Fundus fluorescein angiography; ICG: Indocyanine angiography; RAP: Retinal arterial proliferates.

Tubercular granulomas are the most well recognized phenotype of intraocular tuberculosis (IOTB), and present as yellowish subretinal elevated lesions often accompanied by an exudative retinal detachment (RD). In experimental models of IOTB, these granulomas were found to show overexpression of vascular endothelial growth factor (VEGF). It has been proposed that increased levels of VEGF may be responsible for the vascualarization of these granulomas. Moreover, pharmacological inhibition of the VEGF pathway may limit the spread of Mycobacterium tuberculosis (Mtb) infection causing regression of the new vessels, and thus forms the basis of newly emerging concepts in considering host directed therapies over the usual pharmacological anti-tubercular therapy (ATT) that has been the standard of care for over six decades.

The use of ATT and oral corticosteroids in the management of tubercular granulomas has been well documented in the past. In recent years, a number of case reports have reported successful use of anti-VEGF therapy along with the standard care in the treatment of tubercular granulomas.

To the best of our knowledge, pre- and post-treatment levels of VEGF-A in the aqueous humour of patients with tubercular granulomas have not been studied. We report pre and post treatment results of VEGF-A levels in 10 consecutive patients with intraocular tubercular granulomas who showed a prompt regression with weekly intravitreal injections of anti-VEGF bevacizumab and moxifloxacin along with the usual standard of care ATT and oral corticosteroids. A correlation was done of their clinical regression with the intraocular aqueous levels of VEGF-A.

**ARTICLE HISTORY**

Received 16 March 2021
Revised 25 October 2021
Accepted 31 October 2021

**KEYWORDS**

Tubercular granulomas; intravitreal anti-vascular endothelial growth factor (anti-VEGF); bevacizumab; moxifloxacin.

**CONTACT** Manisha Agarwal @ agarwalmanshi@yahoo.co.in; Vitreoretina Services, Dr Shroff’s Charity Eye Hospital, 5072, Kedarnath Road, Daryaganj, New Delhi 110002, India

© 2021 Taylor & Francis Group, LLC
Material and methods

All consecutive patients between January 2017 and January 2020 who presented with intracranial tuberculosis granulomas at the uvea clinic of a tertiary eye care hospital in North India were included in the study. All these patients met the diagnostic criteria for IOTB according to the classification by Gupta et al. The institutional ethics committee approval was obtained and the study adhered to the tenets of the Declaration of Helsinki. An informed consent was obtained from all the patients. A detailed history of any exposure to pulmonary tuberculosis (TB) was taken. All patients underwent complete hemogram with erythrocyte sedimentation rate (ESR), Mantoux test, contrast enhanced computed tomography (CECT) of the chest and other relevant laboratory investigations to rule out other infectious etiologies. A thorough systemic examination was carried out by an in-house physician. Optical coherence tomography (OCT) and color fundus photo were done at baseline and after every injection. Fundus fluorescein angiography (FFA) and indocyanine green angiography (ICGA) were performed at the discretion of the treating clinician. All the patients were treated with intravitreal injection of anti VEGF bevacizumab (1.25 mg/0.95 ml of label use) and momiflucaric (500 µg/0.1 ml of label use) under topical anesthesia and aseptic precautions, along with four drug ATT and oral corticosteroids (1-1.5 mg/kg/day). Weekly intravitreal injections were continued till there was a clinical resolution of the granulomas and complete resorption of the subretinal fluid (SRF) on OCT. Complete regression of the granuloma was defined as flattening of the granuloma with normalization of the contour of the overlying retinal layers with or without choroid-retinal atrophy (CRA) and resorption of the overlying SRF. Patients who were already receiving ATT therapy for pulmonary or extrapulmonary TB were not excluded from the study.

Anterior chamber paracentesis of the aqueous fluid (0.1 ml) was done immediately after injecting the drugs, thereby normalizing the intracocular pressure. The aqueous fluid sample thus collected in a sterile syringe was packed, labelled and then transported in an insulated box with dry ice to the laboratory. The samples were subjected to sandwich enzyme immunoassay (ELISA) for analysing intravitreal VEGF-A levels. VEGF-A levels were calculated by using human VEGF antibody pair kit (Invitrogen; 10 plate Format; Lott*: 656073; Catalog#:CH0113). The linear range of detection was 2–200 pg/ml (picograms/milliliter).

Polymerase chain reaction (PCR) for the Mtb genome was performed in five patients (anterior chamber sample in four and vitreous sample in one). PCR was not done in the other five patients as four were already receiving ATT at the time of presentation and one patient had financial constraints. A positive Mantoux test, PCR detecting Mtb genome and findings on CECT chest helped in ruling out sarcoidosis.

Extraction of DNA from Patient Sample

Vitreous and aqueous samples were analyzed for Mtb genome detection. Initial sample handling was conducted in BSL-3 facility and the entire DNA was isolated using MasterPure™ Complete DNA and RNA Purification Kit (Epicentre–Lucigen, Cat No. MC85200). DNA was also isolated from M. tuberculosis, H37Rv strain, culture. The yield and quality (ratio of absorption at 260 and 280 nm) of DNA product was measured using NaneDrop™ One (Thermo Fisher Scientific, ND-ONE-W4).

Detection of M. Tuberculosis DNA Using Real-Time PCR and TaqMan Probes

Two probes were designed (Table 1) for detection of M. tuberculosis gene markers, i.e. MPB 64 (NC_018163; Rev 1987c) and IS6110 (X52471). The probes were conjugated with 5’SAM and 3’TAMRA. A real-time PCR reaction (20 µl, microtiter) was set up using Takyon® Rox Probe MasterMix dTTP Blue (Eurogenetec, Cat. No. UF-RFMT-B0701), 250 nanomole (nm) probe, 300 nm forward and reverse primers, and 5 µl DNA. The reaction was performed in Mastercycler® ep realplex® (Eppendorf AG Hamburg, Cat. No. 6002 01796). The following thermal cycling specifications were performed 3 minutes at 95°C and 40 cycles each for 1 second at 95°C, 45 seconds at 53°C (TaqMan), 61°C (IS6110), and 30 seconds at 72°C. All reactions were run in duplicate or triplicate form. The DNA was diluted so that 5 µl contained 10⁵–10⁷ copies. A standard curve was plotted between the copy number and control value from real-time PCR to calculate the bacterial load in patient samples.

Results

A total of 10 eyes of 10 patients were included in the study. Eight patients were females and 2 patients were males. The mean age of presentation was 25.9 + 12.27 years (5-51 years). There was a past history of pulmonary tuberculosis in 6 out of 10 patients. Left eye was affected in 7 out of 10 patients. Anterior uveitis (SUN classification) was present in 6 patients. Varying grades of vitritis was found in all the patients. Eight patients presented with a choroidal granuloma and two patients with optic nerve head (ONH) granuloma. Multiple patches of choroiditis extending till the equator were noted along with ONH granuloma in one patient. Exudative RD with
### Table 2. Clinical profile of patients with tubercular granuloma.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age</th>
<th>Sex</th>
<th>Eye</th>
<th>TB</th>
<th>Anterior segment</th>
<th>Posterior segment</th>
<th>Baseline BCVA</th>
<th>Final BCVA</th>
<th>Mantoux (mm)</th>
<th>CECT Chest</th>
<th>PCR</th>
<th>ATT</th>
<th>Corticosteroid</th>
<th>No of injections</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>F</td>
<td>Yes</td>
<td>Quiet</td>
<td>Vittis, Choroidal granuloma, exudative RD</td>
<td></td>
<td>6/18, N17</td>
<td>6/6, N6</td>
<td>16x18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>M</td>
<td>No</td>
<td>Quiet</td>
<td>Vittis, Choroidal granuloma</td>
<td></td>
<td>6/36, N24</td>
<td>6/6, N6</td>
<td>1x1</td>
<td>Normal study</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>F</td>
<td>Right</td>
<td>No</td>
<td>Quiet</td>
<td>Vittis, Choroidal granuloma</td>
<td></td>
<td>6/9, N6</td>
<td>6/6, N6</td>
<td>2x2</td>
<td>Normal study</td>
<td>Positive, Aqueous sample</td>
<td>Yes</td>
<td>Oral</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>F</td>
<td>Left</td>
<td>No</td>
<td>Flare+2, cells+2</td>
<td>Vittis, ONH granuloma, exudative RD, Choroidal Per-vasculitis</td>
<td></td>
<td>HM</td>
<td>6/24, N12</td>
<td>18x20</td>
<td></td>
<td>Active Roch’s</td>
<td>Positive, Aqueous sample</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>51</td>
<td>F</td>
<td>Left</td>
<td>Yes</td>
<td>Flare+1, cells+1, KP+</td>
<td>Vittis, ONH granuloma, exudative RD</td>
<td></td>
<td>3/60, N36</td>
<td>6/18, N18</td>
<td>20x25</td>
<td>Active Roch’s</td>
<td>Positive, Aqueous sample</td>
<td>Yes</td>
<td>Topical, Oral</td>
</tr>
<tr>
<td>6</td>
<td>28</td>
<td>F</td>
<td>Right</td>
<td>No</td>
<td>Flare+1, cells+1, 360 P.I. Scleritis</td>
<td>Vittis, Choroidal granuloma, exudative RD</td>
<td></td>
<td>HM</td>
<td>HM</td>
<td>32x35</td>
<td>Normal study</td>
<td>Positive, Vitreous sample</td>
<td>Yes</td>
<td>Topical, Oral</td>
</tr>
<tr>
<td>7</td>
<td>17</td>
<td>F</td>
<td>Left</td>
<td>Yes</td>
<td>Flare+1, cells+1</td>
<td>Vittis, Choroidal granuloma, exudative RD</td>
<td></td>
<td>HM</td>
<td>HM</td>
<td>22x22</td>
<td>Active Roch’s</td>
<td>Not done</td>
<td>Yes</td>
<td>Topical, Oral</td>
</tr>
<tr>
<td>8</td>
<td>22</td>
<td>F</td>
<td>Left</td>
<td>Yes</td>
<td>Quiet</td>
<td>Vittis, Choroidal granuloma</td>
<td></td>
<td>6/60, N36</td>
<td>6/18, N12</td>
<td>20x20</td>
<td>Active Roch’s</td>
<td>Not done</td>
<td>Yes</td>
<td>Oral</td>
</tr>
<tr>
<td>9</td>
<td>28</td>
<td>F</td>
<td>Left</td>
<td>Yes</td>
<td>Flare+2, cells+2</td>
<td>Vittis, Choroidal granuloma</td>
<td></td>
<td>HM</td>
<td>6/6, N6</td>
<td>20x22</td>
<td>Active Roch’s</td>
<td>Not done</td>
<td>Yes</td>
<td>Topical, Oral</td>
</tr>
<tr>
<td>10</td>
<td>36</td>
<td>M</td>
<td>Right</td>
<td>Yes</td>
<td>Flare+2, cells+2</td>
<td>Vittis, Choroidal granuloma</td>
<td></td>
<td>3/60, N36</td>
<td>28x30</td>
<td></td>
<td>Active Roch’s</td>
<td>Positive, Aqueous sample</td>
<td>Yes</td>
<td>Topical, Oral</td>
</tr>
</tbody>
</table>

SRF was found in 8 patients. Eight patients reported a positive Mantoux test. CECT chest was suggestive of active pulmonary TB in seven patients. PCR detected 66b-genome in four aqueous samples and one vitreous sample. Four drug ATT was started in five patients and in the other five patients the ongoing ATT was continued, for a minimum duration of 9 months (9–12 months) (Table 2).

At baseline presentation, 9 patients had best corrected visual acuity (BCVA) <6/36 (Snellen’s chart) and one patient with 6/9. At the last follow-up, four patients had BCVA 6/6, two with 6/18 and four patients < 6/24. The mean duration of follow-up was 13.8 ± 7.0 months (9–24). At the last follow-up, complete regression of the granuloma with CRA and resorption of the SRF was seen in all the patients.

Case 1 had a paradoxical worsening after starting ATT and was treated with intravenous methyl prednisolone (IVMP) following which complete regression of the granuloma was seen. Case 7 developed total rhegmatogenous RD for which pars plana vitrectomy with silicone oil injection was performed.

The mean baseline VEGF-A level was 1004.27 ± 411.40 pg/ml (401.33–1688.95). The mean VEGF-A level at the time of last injection was 27.62 ± 46.86 pg/ml (6.89–131.83). A significant decrease in the VEGF-A level was found with successive intravitreal injections. Table 3 shows the correlation of the VEGF-A levels with the clinical response of tubercular granulomas.

**Case reports**

**Case 1**

A 24-year-old female presented with diminution of vision in the left eye for last 5 days. She was diagnosed with pulmonary TB and was on ATT for the last 2 months. BCVA in the right eye was 6/6, N6 and in the left eye 6/36, N12. Right eye fundus was within normal limits. Left eye fundus showed a large choroidal granuloma measuring 3 x 6 mm in the superior quadrant with intraretinal hemorrhage and SRF reaching till the macula. The disc was hyperemic with surrounding granuloma and a small 1 x 1 mm choroidal granuloma was noted inferotemporal to the disc (Figure 1). OCT through the macula showed SRF and transeptal through the superior granuloma showed choroidal bump with SRF and intraretinal cystic spaces. Mantoux test was positive (18x18mm). CECT chest showed fibro-parenchymal lesion in the left upper lobe and calcified lymph nodes bilaterally suggestive of active Koch’s. ATT was continued and oral corticosteroids (1.5 mg/kg/day) were added. An intravitreal injection of bevacizumab and mexitoxifacin was given. Baseline VEGF-A was analyzed as 927.56 pg/ml. At 2-weeks follow-up, extensive CRA was seen in the area of previously noted granuloma. However, a new granuloma was seen at the temporal edge of the CRA corresponding to the healed superior granuloma, extending into the macular area and threatening the fovea. This was diagnosed as a paradoxical reaction and treated with IVMP 1 gm/kg for 3 days followed by high dose oral corticosteroids (2 mg/kg/day) along with a repeat intravitreal injection. VEGF-A level was analyzed as 422.16 pg/ml after the first intravitreal injection. Subsequent follow-up at 2 weeks, BCVA in the left eye improved to 6/6, N6. Fundus showed mild disc hyperemia, complete regression of the granuloma along with CRA and pigmentation and few hard exudates at the macula. OCT showed a normal foveal contour with complete resorption of the fluid.

**Case 2**

Case 2 (33 years, male) and case 3 (22 years, female) presented with unicocular diminution of vision. Case 2 had an exposure of pulmonary TB. In both the patients, on fundus examination there was presence of a choroidal granuloma with vitritis along with perivascularis in case 3. Mantoux test was negative and CECT chest was normal in both the patients. PCR of the aqueous sample was positive for Mtb genome for case 3 and was not done for case 2 due to financial constraints. Both the cases were diagnosed as possible ocular TB. ATT and oral corticosteroids (1 mg/kg/day) were started for both the patients by our in-house physician. Two intravitreal injections of bevacizumab and mexitoxifacin were administered at a weekly interval. Baseline VEGF-A level in case 2 and 3 was 1688.95 pg/ml and 601.32 pg/ml which decreased to 1140.70 pg/ml and 176.74 pg/ml respectively after one intravitreal injection. In case 2, the choroidal granuloma completely melted away and patient gained BCVA of 6/6, N6 (Figure 2). In case 3, the patient gained BCVA of 6/6, N6 and regression of the granuloma was seen with CRA and pigmented scarring and hard exudates at the macula (Figure 3).

**Case 4**

A 5-year-old girl presented with diminution of vision in the left eye for the last 2 months. She gave a history of cough with expectoration. BCVA in the right eye was 6/6, N6 and left eye was hand movements (H) close to face. Fundus examination of the left eye showed a large granuloma infiltrating the optic nerve head with multiple patches of choroiditis extending till the equator (Figure 4). Mantoux test was positive (18x20 mm) and CECT of the chest showed bilateral multiple ill-defined centrilobular nodules with surrounding ground glass opacification and multiple necrotic discrete to conglomerate nodoidal and hilar lymph nodes suggestive of active pulmonary Koch’s. She was started on four drug ATT along with oral corticosteroids (1 mg/kg/day). PCR was positive for Mtb genome. Four intravitreal injections of bevacizumab and mexitoxifacin were administered on a weekly interval. Baseline VEGF-A level was 667.82 pg/ml. It decreased to 376.78 pg/ml, 224.30 pg/ml and 131.83 pg/ml respectively after successive intravitreal injections. The O/N granuloma was found to regress with each injection. Follow-up at 8 months on the completion of ATT, her vision improved to 6/24, N12. Fundus showed mild pallor of the disc with peripapillary CRA and complete regression of the granuloma.

**Case 5**

A 51-year-old female complained of diminution of vision in both the eyes for the last 3 months. She had a history of pulmonary TB fifteen years back for which she had taken
## Table 3. Correlating VEGF-A levels with clinical response of TB granulomas.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Parameters</th>
<th>1st Injection</th>
<th>2nd Injection</th>
<th>3rd Injection</th>
<th>4th Injection</th>
<th>1 month after last injection</th>
<th>Additional Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Size: Peripheral 1x1/posterior</td>
<td>Regressed</td>
<td>Regressed Paradoxal worsening</td>
<td>Regressed</td>
<td>Regressed</td>
<td>-</td>
<td>IVMPE</td>
</tr>
<tr>
<td></td>
<td>SRF</td>
<td>Present</td>
<td>Decreased</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>CRA</td>
<td>Absent</td>
<td>Present</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>VEGF-A</td>
<td>927.56</td>
<td>432.16</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>ATT</td>
<td>8 weeks</td>
<td>9 weeks</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Size: Peripheral 1x1/posterior + Posterior</td>
<td>Regressed</td>
<td>Regressed Paradoxal worsening</td>
<td>Regressed</td>
<td>Regressed</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>SRF</td>
<td>Absent</td>
<td>Absent</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>CRA</td>
<td>Absent</td>
<td>Absent</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>VEGF-A</td>
<td>1688.95</td>
<td>1140.70</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>ATT</td>
<td>12 weeks</td>
<td>12 weeks</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Size: Peripheral + posterior</td>
<td>2x3/posterior + posterior</td>
<td>2x3/posterior + posterior</td>
<td>2x3/posterior + posterior</td>
<td>2x3/posterior + posterior</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>SRF</td>
<td>Absent</td>
<td>Absent</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>CRA</td>
<td>Absent</td>
<td>Absent</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>VEGF-A</td>
<td>401.32</td>
<td>176.74</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>ATT</td>
<td>Started</td>
<td>1 week</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td>4</td>
<td>Size: ONH granuloma</td>
<td>Regressing</td>
<td>Regressing</td>
<td>Regressing</td>
<td>Regressing</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>SRF</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>CRA</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>VEGF-A</td>
<td>667.32</td>
<td>378.78</td>
<td>224.30</td>
<td>131.83</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>ATT</td>
<td>Started</td>
<td>1 week</td>
<td>2 weeks</td>
<td>3 weeks</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td>5</td>
<td>Size: ONH granuloma</td>
<td>Regressing</td>
<td>Regressing</td>
<td>Regressing</td>
<td>Regressing</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>SRF</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>CRA</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>VEGF-A</td>
<td>787.91</td>
<td>272.02</td>
<td>156.87</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>ATT</td>
<td>Started</td>
<td>1 week</td>
<td>2 weeks</td>
<td>3 weeks</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td>6</td>
<td>Size: ONH granuloma</td>
<td>Regressing</td>
<td>Regressing</td>
<td>Regressing</td>
<td>Regressing</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>SRF</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>CRA</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>VEGF-A</td>
<td>1436.20</td>
<td>814.80</td>
<td>482.20</td>
<td>52.67</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>ATT</td>
<td>Started</td>
<td>1 week</td>
<td>2 weeks</td>
<td>3 weeks</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td>7</td>
<td>Size: ONH granuloma</td>
<td>Regressing</td>
<td>Regressing</td>
<td>Regressing</td>
<td>Regressing</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>SRF</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>CRA</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>VEGF-A</td>
<td>1372.95</td>
<td>262.49</td>
<td>46.66</td>
<td>6.9</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>ATT</td>
<td>Started</td>
<td>1 week</td>
<td>2 weeks</td>
<td>3 weeks</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td>8</td>
<td>Size: ONH granuloma</td>
<td>Regressing</td>
<td>Regressing</td>
<td>Regressing</td>
<td>Regressing</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>SRF</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>CRA</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>VEGF-A</td>
<td>742.80</td>
<td>257.90</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>ATT</td>
<td>Started</td>
<td>1 week</td>
<td>2 weeks</td>
<td>3 weeks</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td>9</td>
<td>Size: ONH granuloma</td>
<td>Regressing</td>
<td>Regressing</td>
<td>Regressing</td>
<td>Regressing</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>SRF</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>CRA</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>VEGF-A</td>
<td>1180.70</td>
<td>874.81</td>
<td>391.50</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>ATT</td>
<td>Started</td>
<td>1 week</td>
<td>2 weeks</td>
<td>3 weeks</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td>10</td>
<td>Size: ONH granuloma</td>
<td>Regressing</td>
<td>Regressing</td>
<td>Regressing</td>
<td>Regressing</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>SRF</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>CRA</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>VEGF-A</td>
<td>534.27</td>
<td>186.20</td>
<td>97.83</td>
<td>84.82</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>ATT</td>
<td>Started</td>
<td>1 week</td>
<td>2 weeks</td>
<td>3 weeks</td>
<td>-</td>
<td>Oral steroids</td>
</tr>
</tbody>
</table>

Size in millimeter(mm), SRF: Subretinal fluid, CRA: Chorioretinal atrophy, VEGF: Vascular endothelial growth factor in picograms/milliliter (pg/ml), IVMPE: Intravenous Methy prednisolone, FPV: Pars plana vitrectomy, SIG: Silicon oil

ATT. BCVA in the right eye was 6/9, N6 and in the left eye 3/60, N36. Anterior segment of the right eye showed old keratic precipitates (KP). Left eye showed cells+1, flare+1, mutton fat KP’s, and posterior subcapsular cataract. Fundus of the right eye showed peripapillary CRA with pigmented scarring and the left eye showed a large granuloma infiltrating the ONH with intraretinal hemorrhage and peripapillary serous retinal detachment involving the macula (Figure 5). OCT through the disc confirmed a granuloma with surrounding SRF detaching the macula. Mantoux test was positive (20x25 mm) and CECT chest showed a focal area of subsegmental collapse with pulled up major fissure in the apical-posterior segment of the left upper lobe suggestive of old Koch’s and a small local area of fibro-paranchymal lesion in the apical segment of the right
Figure 1. Case 1: (a) Left eye fundus photo showing a large choroidal granuloma 3 × 6 mm (red arrow), hyperemic disc with surrounding granuloma (green arrow) and a 1 × 1 mm choroidal granuloma inferotemporal to the disc (yellow arrow). (b) OCT macular scan showing intraretinal cystic spaces (yellow arrow) and subretinal fluid (red arrow). (c) OCT scan through the superior granuloma showing choroidal bump with intraretinal cystic spaces (yellow arrow) and subretinal fluid (red arrow). (d) Fundus photo showing regression of the granuloma (yellow arrow) 2 weeks after the first injection with a new lesion due to paradoxical worsening (red arrow). (e) OCT macular scan showing subretinal fluid (yellow arrow). (f) OCT scan through the new lesion showing choroidal bump (yellow arrow) with subretinal fluid (red arrow). (g) Fundus photo showing completely regressed granuloma (red arrow) with hard exudates at the macula (green arrow) after IVMP and second injection. (h) OCT macular scan showing normal foveal contour. (i) OCT scan through the granuloma showing normal choroidal structure.

Figure 2. Case 2: (a) Left eye fundus photo showing a 3 × 6 mm choroidal granuloma in the superior quadrant (red arrow). (b) and (c) Fundus photo showing melting of the granuloma after the first and second injections, respectively. (d) Fundus photo showing complete disappearance of the granuloma at 9-month follow-up.

Figure 3. Case 3: (a) Right eye fundus photo showing a 3 × 4 mm choroidal granuloma along the inferior arcade (red arrow). (b) and (c) Fundus photo showing regressing granuloma (red arrow) along with hard exudates at the macula (yellow arrow) after the first and second injections, respectively. (d) Fundus photo showing regressed choroidal granuloma (red arrow) at 9-month follow-up.
Figure 4. Case 4: (a) Left eye fundus photo showing ONH granuloma (red arrow) with surrounding choroiditis (green arrow) and peri-vasculitis (yellow arrow). (b–e) Fundus photos showing regression of the granuloma with resolving choroiditis and peri-vasculitis after the first, second, third, and fourth injections, respectively. (f) Fundus photo showing completely regressed ONH granuloma with resolving peri-vasculitis (yellow arrow) at 3-month follow-up. (g) Fundus photo at 9-month follow-up showing normal ONH contour (red arrow).

Figure 5. Case 5: (a) Left eye fundus photo showing an ONH granuloma with intraretinal hemorrhage (yellow arrow). (b) OCT scan through the ONH showing granuloma (yellow arrow) with surrounding subretinal fluid (red arrow). (c) OCT macular scan showing subretinal fluid (yellow arrow). (d) Left eye fundus photo showing complete regression of the granuloma after three injections. (e) OCT scan showing normal ONH contour. (f) OCT macular scan showing complete resorption of the subretinal fluid.

upper lobe suggestive of active Koch’s. PCR was positive for Mtb genome. She was started on four-drug ATT, oral corticosteroids (1.5 mg/kg/day) and topical prednisolone acetate eye drops (1%) with atropine (1%). Three intravitreal injections of bevacizumab and moxifloxacin were administered at a weekly interval. Baseline VEGF-A level was 787.91 pg/ml which decreased to 272.62 pg/ml and 135.67 pg/ml subsequently after repeat injections. Complete regression of the granuloma with resorption of the SRF was noted. OCT showed a normal contour of the disc and the macula.

Discussion
In our series of consecutive 10 eyes of 10 patients with intraocular tubercular granulomas, in addition to the usual ATT and oral corticosteroids, weekly injections of anti-VEGF bevacizumab and moxifloxacin led to a prompt regression of these granulomas that included eight choroidal and two ONH granulomas. Five of these patients, who had not received prior ATT, in whom aqueous humour was subjected to PCR showed the presence of the Mtb genome in the intraocular fluid, confirming the tubercular etiology of these granulomas. We also
found very high levels of VEGF-A in the pretreatment aqueous humour. The VEGF-A levels decreased substantially in these eyes following the weekly intravitreal therapy and correlated significantly with the regression of the granulomas. We thus provide evidence for the rational use of the anti-VEGF therapy in the management of intracranial tubercular granulomas. The monthly use of anti-VEGF therapy is currently the gold standard for neovascular age-related macular degeneration (AMD) and macular oedema due to diabetic retinopathy and retinal vascular occlusion is based on the presence of VEGF in the ageusia/vitrous humour of these patients. However, we observed much higher: VEGF-A levels in tubercular granulomas than have been reported in the aforementioned retinal diseases. Hence, we feel that a much higher frequency of the anti-VEGF therapy was required in our patients. The progressive decrease in the VEGF levels following weekly injections has thus justified this approach.

VEGF is a known biomarker for active TB disease in pulmonary as well as extrapulmonary sites, to monitor disease severity, bacterial burden, and therapeutic responses in pulmonary TB. Matsuyama et al. analyzed the serum VEGF levels (722.6 ± 362.2 pg/ml) in patients with active pulmonary TB and found them significantly higher than in old treated TB patients (185.1 ± 158.4 pg/ml). The highest serum VEGF level was 1300 pg/ml which decreased to <100 pg/ml 6 months after ATT. They showed that the serum VEGF levels of patients with active pulmonary TB decreased parallel to improvement of the disease.

A vision threatening paradoxical worsening of IOTD due to an immunological reaction is a major feature of starting ATT which requires stepping up of oral corticosteroids and at times needs intravenous corticosteroid therapy. This is well demonstrated by case 1 of our series. However, Jain et al. have reported a case of paradoxical worsening in a HIV-infected patient with tubercular granuloma that did not respond to oral corticosteroids but showed an excellent response to i.v. injections of bevacizumab. Agrawal et al. reported a case in which even after 3 months of ATT there was no regression of the granulomas which was associated with an exudative RD. However, three weekly injections of bevacizumab and mofirofloxacin led to a complete regression of the granulomas with resolution of the exudative RD.

In the last decade, a few case reports have been published highlighting the use of intravitreal anti-VEGF agents as monotherapy or as adjunct to ATT and oral corticosteroids for treating tubercular granulomas. Bansi et al. and Babu et al. each treated a case of vascularized tubercular granulomas with monthly intravitreal injections of bevacizumab along with ATT and corticosteroids leading to regression of the granuloma and resolution of exudative RD. Bansi et al. in their case have also shown a prompt regression of the recurrent granulomas which occurred after one year of stopping ATT and was treated with two bevacizumab injections alone thereby maintaining the remission of the granuloma. Invernizzi et al. have reported the first case of an ONH tubercular granuloma with surrounding SRD successfully treated with monthly injections of bevacizumab along with ATT and oral corticosteroids. Jain et al. have reported complete regression of a vascularized tubercular granuloma with single intravitreal injection of ranibizumab without adding ATT as they did not find any evidence of systemic TB. In contrast, we started ATT without any evidence of systemic TB in cases 2 and 3 based on the clinical signs, as suggested by Gupta et al. 13

Ocular TB is a form of extrapulmonary TB presenting as uveitis in TB-endemic countries like India. The classic histopathological finding in IOTD is epithelioid cell granuloma with a central area of caseation necrosis. Datta et al. 19 have shown that in both human and rabbit tubercular granulomas, VEGF is most highly expressed in the inner macrophage layer that surrounds the necrotic core. They also noted that vasculature, with the highest density in the periphery of these granulomas, was both structurally, morphologically, and functionally abnormal. Further they have shown that bevacizumab normalizes the granuloma vasculature, reduces hypoxia, and also enhances the small molecule delivery of anti-TB drugs.

A multidrug therapy regimen of ATT should not logically allow multidrug resistant TB (MDR-TB) to emerge. Yet, it is a well phenomenon in pulmonary TB and other extrapulmonary sites. Moreover, reports of MDR-TB are emerging in ophtalmic literature and posing a major therapeutic challenge that calls for innovative host directed therapies. 20-24 Of all the drugs that are used to treat TB, isoniazid is the only bactericidal drug which blocks the cell wall synthesis of the dividing Mtb, and its efficacy is determined directly by the rate of the multiplication of Mtb. 25 Also, isoniazid is not effective against non-multiplying or dormant Mtb. Wyama et al. 26 demonstrated that Mtb stops multiplying and goes into dormancy in hypoxic conditions.

It has been proposed that one of the main factors in the emergence of MDR-TB may be the abnormal vessels that do not allow the ATT drugs to diffuse equally in all the parts of the granuloma. This effectively reduces the ATT to a monotherapy thereby enhancing the chances of developing MDR-TB. Using anti-VEGF drugs such as bevacizumab ensures equal distribution of all the therapeutic agents in the granuloma significantly reducing the chances of MDR-TB. 27

The anti-TB drugs were introduced for the treatment of TB without knowing the pharmacokinetics and their differential concentration in various cellular components of the tubercular granuloma. The rationale for using multiple drugs in ATT is due to the action of various drugs on different phases of Mtb. 28 Tubercular granulomas show a favourable but slow response when treated with ATT. 29 There have been reports of rapid diminution of vision with early onset of intraretinal and subretinal neovascularization due to arteriovenous communication leading to the formation of retinal arterial proliferans (RAP) in these granulomas. 29,30 This may lead to a painful blind eye requiring a removal while being on ATT. 30

In recent years, use of high-performance liquid chromatography coupled to tandem mass spectrometry in rabbit model of TB has shown that compared to the plasma levels, mofirofloxacin is preferentially accumulated in the macrophages with a high intracellular to extracellular ratio compared to other anti-TB drugs like isoniazid, rifampicin, and pyrazinamide. 31 However, it diffuses poorly into the necrotic center of the granuloma which can be penetrated only
by pyrazinamide. Therefore, we used intravitreal moxifloxacin to target the most active component of the tubercular granuloma, that is activated macrophages harboring Mtb to facilitate a quick elimination of the organisms.

Our case series differs in the following ways from what has been previously reported, firstly we gave a combination of intravitreal anti-VEGF bevacizumab and moxifloxacin injection in comparison to only anti-VEGF injections used in the past. Secondly, previous case reports gave monthly anti-VEGF injections in the management of tubercular granulomas, whereas we gave weekly injections in all our patients. The rationale for repeating the anti-VEGF injection every week till the regression of the granulomas was the five times higher mean baseline intraocular VEGF-A level 1004.27 ± 411.40 pg/ml (401.32–1488.95) as compared to the mean baseline VEGF-A level 179.7 ± 88.4 pg/ml (74.5–521.6) in patients with neovascular AMD, and that the half-life of intravitreal bevacizumab ranges between 2.5 and 3.3 days in non-vitreotomised eyes that may be further shortened due to the breakdown of the blood-retinal barrier secondary to the inflammation leading to early washout of the drug. Thirdly, we have also correlated the clinical regression in each case with the corresponding decreasing levels of the VEGF-A, which has never been reported earlier.

It is all but intuitive that efforts should be made not only to restore the vision of the patient quickly but also normalize the vasculature of the tubercular granulomas so that the ATT drugs effectively reach the granulomas and regress it besides preventing the emergence of MDR-TB and dormant-TB in the ocular tissues. In view of better understanding of the diffusion of ATT into the granuloma, it may be speculated that purposefully restricting to the conventional treatment with ATT and oral corticosteroids may allow for a slower response and increase the risk of MDR-TB and dormant-TB with a resultant recurrent and difficult to treat granuloma in the eye.

In view of only anecdotal reports in the literature, and absence of any recommended guidelines for the treatment of tubercular granulomas with anti-VEGF agents, we were driven by our earnest desire to bring about a quick regression of the granulomas and restore the vision of our patients. The question of the most effective frequency of anti-VEGF in these granulomas can be addressed in multicentric large controlled trials, which given the small numbers is not possible to do in single center studies. Our study is at best the proof of a conceptual clinical study and should prompt a controlled clinical large trial in the near future for formulating new guidelines for the management of these vision threatening tubercular granulomas.

Studies have reported the risk of retinal pigment epithelium (RPE) atrophy on repeated intravitreal anti-VEGF injections but this toxic effect has only been found in eyes with neovascular AMD who receive these injections in perpetuity unlike a limited use in our patients. The development of complete RPE and outer retinal atrophy (CORA) is, however, inversely related to the number of anti-VEGF injections. We believe there is a much greater risk of macular scarring and RPE and outer retinal atrophy by delaying the regression of these granulomas by using the conventional treatment of ATT and oral corticosteroids.

There is an inherent risk of endophthalmitis with intravitreal injections irrespective of their frequency and thus calls for a meticulous aseptic technique. We followed the standard protocols that are universally recommended and accepted all over the world. However, the risk of infection has not deterred the use of intravitreal injections that are considered as the most frequent intervention in the entire world of medicine.

In our study, we collected anterior chamber sample for VEGF analysis, though better would have been to collect the vitreous sample that possibly would have shown a much higher VEGF level, as the granuloma is in the posterior segment of the eye. However, this would have required an active intervention in the form of a vitreous biopsy or vitreous aspiration multiple times for which we did not get an ethical clearance.

The limitations of this study are a small cohort, single center study, non-randomized with absence of a control arm, and inability to correlate VEGF levels with findings on FFA or ICGA as they were not performed in all the patients.

**Conclusion**

Very high levels of VEGF-A are found in patients with intravitreal tubercular granulomas. Intravitreal injections of anti-VEGF along with moxifloxacin may be beneficial as an adjunct to ATT and oral corticosteroids for a prompt regression of these tubercular granulomas. More frequent than monthly injections may be required in comparison to patients with neovascular AMD. The formulation of treatment guidelines for tubercular granulomas may require multicentric controlled trials with a larger number of patients in future.

**Acknowledgments**

Amit Gupta
Professor Emeritus
PGIMER, Chandigarh 160012, India
Email: dramosgupta@gmail.com

**Disclosure statement**

No potential conflict of interest was reported by the author(s).

**Funding**

The author(s) reported there is no funding associated with the work featured in this article.

**ORCID**

Munisha Agarwal, MS, DNS (http://orcid.org/0000-0002-2277-061X)

**References**

471


SHORT TERM OUTCOMES OF COMBINED BUCKLE AND SCLERAL IMBRICATION FOR COMPLEX RETINAL DETACHMENTS

Introduction:

Retinal detachment in children pose different challenges due to different anatomy, characteristics of the vitreous and associated ocular and systemic conditions. Due to tight adhesions between the vitreous and the retinal surface, no posterior vitreous detachment, higher chances of PVR; anatomical success rates of vitrectomy (62-88%) aren’t as good as that in adults. Scleral buckle is hence considered a first choice as there is minimal vitreous manipulation, less cataract formation and avoids the need of tamponade and positioning. However, scleral buckle is reserved for cases without significant PVR and other ocular anomalies. In cases of complex retinal detachment like those with a combined mechanism of retinal folds, traction and rhegma, the success rates with scleral buckle and PPV is poor.

Scleral imbrication was described first in 1958 as the primary procedure for
repairing retinal detachment before vitrectomy was invented.\textsuperscript{2} With the advent of procedures like buckle and vitrectomy, imbrication was no longer done primarily in retinal detachment. Recently, imbrication was used to correct myopic foveoschisis and myopic macular hole with the thought that scleral shortening caused by imbrication causes the hole to close and schisis to collapse.\textsuperscript{3,4} With the same principle we used modified scleral imbrication (imbrication with scleral buckle) to manage complex retinal detachment in children where in the surgeon’s view buckle and/or vitrectomy would have poor anatomical results.

**Methods:**

It was a retrospective, interventional study of children (<16 years) presenting with complex retinal detachment. The study was conducted at a tertiary eye care institute in South India between October 2020 to December 2021. The study adhered to the declaration of Helsinki and was approved by the institutional review board. All the surgeries were done by a single surgeon.

Demographic details including age, gender and the eye involved was noted. Pre-operative primary and secondary diagnosis, pre-operative best corrected visual acuity (BCVA), fundus findings were evaluated. All patient underwent ancillary testing like wide field fundus photography or ultrasonography whenever deemed necessary.

Surgical technique: Diagnosis was confirmed and rhegma was tried to be located under general anesthesia on table before proceeding with surgery. Once the decision of scleral imbrication was taken, 360 degrees conjunctival
peritomy was done and four recti were tagged. Rhexis or site of suspected rhexis was located and appropriate buckle was chosen. Site of imbrication was decided on the basis of site of rhexis and the extent of retinal detachment. Subretinal external drainage was done either with needle or using cutdown technique. Buckle was then placed and after a betadine wash of all quadrants, the conjunctiva was closed with 7-0 vicryl. Post-operative retinal status was evaluated. Descriptive statistics was used for analysis.

**Results:**

24 eyes of 24 patients were included in the study. Fifteen patients (62.5%) were male. Mean age at surgery was 47.1 months. Retinopathy of prematurity was the most common primary diagnosis causing retinal detachment in 17 of the 24 eyes (70.8%). Eleven of 24 eyes (45.8%) had combined tractional and rhegmatogenous RD, nine (37.5%) had tractional RD and 4 (16.6%) had complex rhegmatogenous RD with PVR. 17 eyes (70.8%) had pre-operative retinal drag and fixed folds.

Imbrication was done in all eyes. Mean number of quadrants imbricated was 2.5 (median = 2). Additional buckle was used in all patients. Twenty one eyes (87.5%) had responded well to the surgery and 19 eyes (79%) had completely attached retina/settled retinal folds without progression post surgery. Failure of the surgery was seen in 3 eyes (12.5%) out of which 1 eye had recurrence causing the need for pars plana vitrectomy. Mean follow up was 197.8 days.

**Discussion:**

Our data showed that the anatomical success rate of scleral imbrication with
buckle in complex retinal detachment of childhood onset is good (87.5%).
The surgical success rates in pediatric RD with one surgery is much lower
than adults and varies between 52 -78%.1 As a result, multiple surgeries
might be required. Anatomical success after multiple interventions is still
poor and ranges between 60-83%. This is much poorer in complex RD’s
where additional tractional component or the presence of retinal folds
makes vitrectomy extremely difficult. Scleral buckle in such cases might not
provide adequate reversal of forces to close the rhegma or flatten the
progressing retinal folds. Scleral imbrication provides additional scleral
shortening and hence aiding in reversing vector forces for retinal re-
attachment.

The study is however, limited due its retrospective nature and lack of
comparative arm. The sample size is small. We evaluated only the short term
outcomes and the long term follow up of the technique is awaited.

**Conclusion:**

To conclude, scleral imbrication with scleral buckle shows encouraging
short term anatomical results in childhood onset complex retinal
detachment. The novel technique provided a new way of managing complex
childhood onset retinal detachments with a single surgery, that otherwise
require multiple vitreoretinal procedures often with unpredictable
outcomes. Long-term outcomes are awaited.

**References:**

1. Al Abdulsalm O, Al Habboubi H, Mura M, Al-Abdullah A. Re-Vitrectomy
versus Combined Re-Vitrectomy with Scleral Buckling for Pediatric

2. SWAN KC. Scleral imbrication for retinal detachment. AMA Arch Ophthalmol. 1959 Jan;61(1):110-4


For patients with **Ocular Discomfort**

**Start with**

Rx **Refresh Tears®**

Mimics Human Tears*¹,²

Formulations balanced with

- **Electrolytes**
- **Viscosity**
- **pH**
- **Osmolarity**

**References:**
1. Simmons et al; Ophthalmic Pract 2002;20(2): 77-80

ALLERGAN INDIA PVT LTD. Level 7, Prestige Obelisk, No.3 Kasturba Road, Bangalore 560 001.
Phone No.: +91-80-4070 7070 | Fax: +91-80-4070 7007 | E-mail: IN-Allergan@Allergan.com