Volume 35 - Issue 2
May - August 2023

ISSN 0976-6677
www.kjophthal.com

KERALA JOURNAL OF OPHTHALMOLOGY





Stem Cells in Glaucoma: A Promising Frontier for Vision Restoration | IOL Opacification: President's Perspective | Ophthalmic Conferences: Time for change? | Prostaglandin Analogues in Ophthalmology | The Kaplan Meir Curve: Interpretation Made Easy

Wolters Kluwer

Medknow

ISSN 0976-6677

Kerala Journal of Ophthalmology

Editorial Board

Editor
Smita Narayanan

Associate Editor
Sinumol. S

Managing Editor
Rajiv Sukumaran

International Editors
Geeta Menon

Azim Siraj

Advisory Board
Anantharaman Giridhar

Sahsranamam V

Charles Skariah

Arup Chakrabarti

Mahadevan K

Section Editors
Sujatha N

Rani Balamurali

Manoj S

Natasha Radhakrishnan

Assistant Editors
Remya Raghavan

Ferzana Mohammed

Remya Edachery

Mentors
Ani Sreedhar

Minu Mathen

Ganesh V Raman

Elizabeth Joseph K

Thomas Cherian

Santosh G Honavar

Mahesh G

C V Anthrayose Kakkanatt

Somasheila Murthy

Emeritus Editors
Anantharaman Giridhar

Krishnankutty

NSD Raju

Ashok Nataraj

Mahadevan K

PI Mohan

Bastin VA

Mahesh G

Sudha V

Gopal S Pillai

Meena Chakrabarti

KE Eapen

Narayanankutty K

Central Picture:

Fate couldn't be kinder. This young man who was impaled on a protruding wire could arrest his fall before the object exited through the opposite eye wall. If the wire had travelled just 4 mm to one side or 1 mm deeper his vision would not have been anywhere near his actual post vitrectomy vision of 6/6.

Photo courtesy: Dr. Biju John, Professor of Ophthalmology, Government Medical College, Kollam, Kerala, India.

Kerala Journal of Ophthalmology

Volume 35 Issue 2 May-August 2023

Contents

Editorial

Ophthalmic conferences: Time for change?
Smita Narayanan 121

Guest Editorials

IOL opacification: My perspective
S. J. Saikumar 123

Exploring the therapeutic potential of stem cells in glaucoma: A promising frontier for vision restoration
Suneeta Dubey, Nisha Sinha 125

Review Article

Ophthalmic prostaglandin analogs revisited - A systematic review of commonly used formulations
Kaberi Biswas Feroze 130

Ophtha Insta

"Ousted little elf"—Secondary glaucoma in Weill-Marchesani syndrome
Devi Karthya 139

Original Articles

Efficacy of topical immunotherapy in the management of Ocular Surface Squamous Neoplasia (OSSN)– A retrospective analysis
Sinumol S. Thulaseedharan, Ajithkumar V Raghavan, Ashwati Sankar, Sujatha N, Sudha Vaikkakara, Devu Krishna T 141

An observational study on the clinical picture of vernal keratoconjunctivitis at a tertiary care center in Western India
Mohini Agrawal, Srujana Dubbaka, Sumedha Vats 149

Evaluation of tacrolimus and cyclosporine in the treatment of vernal keratoconjunctivitis in children
Suresha A. R, Gaargi Shashidhar, Prabhudeva H 155

Parents' perception about children screen time and myopia during covid-19 pandemic
Aksha Shetty, Nehal Naik, Ugam P. S. Usgaonkar 161

A cross-sectional study to determine the relationship between diabetic retinopathy and diabetic nephropathy in type 2 diabetes mellitus patients in South India
Anjali L. Roche, Rajashree S. Prabhu, Indu Govind 168

Awareness and attitude regarding eye donation among undergraduate students of an engineering institution and its implication in Tamil Nadu
Gnaneswaran Subramaniam, Murugan Kumarasamy, Ameenah A. H. Siraja 174

Clinical and microbiologial profile of bacterial and fungal keratitis: A comparison of patients with and without diabetes mellitus
Jincy Mariya Paul, P. T. Jyothi 179

Blind spot in ultrasound central corneal thickness measurement – Central corneal thickness of apex versus central corneal thickness of vertex
Prasanna Venkatesh Ramesh, Sathyan Parthasarathi, Abhinay Ashok, Rajesh Kumar John 187

Macular morphological changes in retinal vein occlusion with macular involvement and their association with macular ischemia
Renuka Rawat, Charudatt Chalisgaonkar, Divya Tripathi, Shashi Jain 194

Case Reports

Malignant glaucoma: A therapeutic challenge
A. Anuradha, M. Vidhya Devi, Rose Mary George, N. Manoj Kumar, Priyam Gupta 198

Hyperacute spontaneous closure of a traumatic macular tear in a middle-aged female
Syed Mohideen Abdul Khadar, Jahnara Jaffar 201

Corneal component surgery: Expanding the indications
Nimisha Nagpal, Pawan Prasher 203

Presumed silicone oil droplets following intravitreal bevacizumab injection
Pradeep Kumar Panigrahi, Jasmita Satapathy, Yamijala Neha Srija 207

Frontalis sling in a bilateral ptosis with external ophthalmoplegia and poor bell's phenomenon: A 5-year follow-up
N. V. Latha, M Vishnupriya 210

Herpes simplex virus-1 associated third cranial nerve palsy in pediatric age group
Suchismita Mishra, Lipika Mehra, Pradeep Kumar Panigrahi, Lulup Kumar Sahoo 215

Bilateral giant dacryocele in a case of Tessier cleft-3
Sahil Agrawal, Sujeeth Modaboyina, Saloni Gupta, Deepsekhar Das 218

A conventional case of herpes zoster ophthalmicus with curious findings
Aravind Yaragani, Kamala Subramanian 220

A rare case of central retinal artery occlusion following severe orbital blowout fracture
Pradeep Kumar Panigrahi, Anita Minj, Priya Gupta, Lipika Mehra 223

Photo Essay

Bilateral persistent pupillary iris membrane mimicking chronic anterior uveitis
Amol Ganvir, Aryamol V. Surendran, Shruti Shirwadkar, Chhaya Shinde 226

Statistics Corner

Comprehending Kaplan–Meier curve
Sandhya Somasundaran 228

Journal Review

Changing trends in the use of anti-vascular endothelial growth factor (anti-VEGF) biosimilars: Insights from the Vitreoretinal Society of India Biosimilars of Anti-VEGF Survey
Dhanya Radhamani Sasidharan 231

Letter to the Editor

Comments on "Amblyopia: Effectiveness of visual screening for early detection in a comparative study between urban and rural children"
Radhika Krishnan RB 234

Kerala Journal of Ophthalmology

General Information

The journal
Kerala Journal of Ophthalmology (KJO), the official publication of Kerala Society of Ophthalmic Surgeons (KSOS) is published as print and online journal.

Abstracting and Indexing information
Baidu Scholar, CNKI (China National Knowledge Infrastructure), EBSCO Publishing's Electronic Databases, Ex Libris – Primo Central, Google Scholar, Hinari, Infotrieve, National Science Library, ProQuest, TdNet, Wanfang Data

The journal is indexed with, or included in, the following:

DOAJ

Information for Authors
There are no page charges for submissions to the journals. Please check http://www.kjophthal.com/contributors.asp for details.

All manuscripts must be submitted online at www.journalonweb.com/kjo.

Subscription Information
Copies are provided free of cost to members of KSOS. A subscription comprises of 3 issues every year. Please include postage.

Annual subscription rates for non-members

Institutional - INR 4650.00 for India and USD 560.00 for outside India
Personal - INR 4650.00 for India and USD 370.00 for outside India
For mode of payment and other details, please visit www.medknow.com/subscribe.asp.

Claims for missing issues will be serviced at no charge if received within 60 days of the cover date for domestic subscribers, and 3 months for subscribers outside India. Duplicate copies cannot be sent to replace issues not delivered because of failure to notify publisher of change of address.

The journal is published and distributed by Wolters Kluwer India Private Limited. Copies are sent to subscribers directly from the publisher's address. It is illegal to acquire copies from any other source. If a copy is received for personal use as a member of the association/society, one cannot resale or give-away the copy for commercial or library use.

The copies of the journal to the members of the association are sent by ordinary post. The editorial board, association or publisher will not be responsible for non receipt of copies. If any member/subscriber wishes to receive the copies by registered post or courier, kindly contact the publisher's office. If a copy returns due to incomplete, incorrect or changed address of a member/subscriber on two consecutive occasions, the names of such members will be deleted from the mailing list of the journal. Providing complete, correct and up-to-date address is the responsibility of the member/subscriber.

Nonmembers: Please send change of address information to wkhlrpmedknow_subscriptions@wolterskluwer.com.

Advertising policies
The journal accepts display and classified advertising. Frequency discounts and special positions are available. Inquiries about advertising should be sent to Wolters Kluwer India Private Limited, advertise@medknow.com.

The journal reserves the right to reject any advertisement considered unsuitable according to the set policies of the journal.

The appearance of advertising or product information in the various sections in the journal does not constitute an endorsement or approval by the journal and/or its publisher of the quality or value of the said product or of claims made for it by its manufacturer.

Copyright
The entire contents of the Kerala Journal of Ophthalmology are protected under Indian and international copyrights. The Journal, however, grants to all users a free, irrevocable, worldwide, perpetual right of access to, and a license to copy, use, distribute, perform and display the work publicly and to make and distribute derivative works in any digital medium for any reasonable non-commercial purpose, subject to proper attribution of authorship and ownership of the rights. The journal also grants the right to make small numbers of printed copies for their personal non-commercial use.

Permissions
For information on how to request permissions to reproduce articles/information from this journal, please visit www.kjophthal.com

Disclaimer
The information and opinions presented in the Journal reflect the views of the authors and not of the Journal or its Editorial Board or the Publisher. Publication does not constitute endorsement by the journal. Neither the Kerala Journal of Ophthalmology nor its publishers nor anyone else involved in creating, producing or delivering the Kerala Journal of Ophthalmology or the materials contained therein, assumes any liability or responsibility for the accuracy, completeness, or usefulness of any information provided in the Kerala Journal of Ophthalmology, nor shall they be liable for any direct, indirect, incidental, special, consequential or punitive damages arising out of the use of the Kerala Journal of Ophthalmology. The Kerala Journal of Ophthalmology, nor its publishers, nor any other party involved in the preparation of material contained in the Kerala Journal of Ophthalmology represents or warrants that the information contained herein is in every respect accurate or complete, and they are not responsible for any errors or omissions or for the results obtained from the use of such material. Readers are encouraged to confirm the information contained herein with other sources.

Address
Editorial Office
Dr. Smita Narayanan
M. S (Ophth), FAICO (Glaucoma)
Regional Institute of Ophthalmology, Thiruvananthapuram, Kerala, India.
Email: drsmita.narendranath@gmail.com
Phone: 9446430633

Published by
Wolters Kluwer India Private Limited.
A-202, 2nd Floor, The Qube, C.T.S. No.1498A/2 Village Marol, Andheri (East), Mumbai - 400 059, India.
Phone: 91-22-66491818
Website: www.medknow.com

Printed at:
Nikeda Art Printers Pvt. Ltd.,
Building No. C/3 - 14,15,16, Shree Balaji Complex, Vehele Road, Village Bhatale, Taluka Bhiwandi, District Thane - 421302, India.

Ophthalmic conferences: Time for change?

We have just finished attending the annual conference of the All-India Ophthalmological Society at Kochi in May and now we are organizing the Drishti 2023, the annual conference of the Kerala Society of Ophthalmic Surgeons at Thrissur in November 2023. Two big events in a span of just over six months! We know and Loannidis has precisely pointed out that "these events come in all sizes, from relatively small, local gatherings, workshops, and symposia to large international mega-congresses that mobilize tens of thousands of clinicians, researchers, exhibitors, and staff to build small-sized towns for a few days."[1] In India itself, hundreds of these events are organized annually and their numbers are burgeoning. The cost of organizing these events is mind boggling and spiraling.

As ophthalmologists, we are persons practicing science. Therefore, the prime objective of an ophthalmic conference is academic. Imparting the recent advances in various subspecialties, creating fora for discussion and consensus in controversial issues, and providing skill-based training are some of the highlights of conferences. Pandey *et al.*[2] consider that apart from imparting education, conferences also enable interaction with peers and opinion-makers which leads to improvement in eye-care delivery and visual outcomes.

Many of us who have always thought that the conferences are for academic advancement have been disturbed by recurring instances of speakers presenting before empty halls or to their co-speakers. Though this was present before, the pandemic exaggerated it. Perhaps nobody wants to learn anything from the speakers because excellent lectures and other related materials are available online. In this era of instant gratification, nobody is willing to sit for 10–15 min through a lecture to dig out points of value from them. The speakers too are grudgingly finding out that the halls for Instruction Courses no longer provide them the "optics to advertise their podium presence." One of the main reasons this is happening is because the demographics of the ophthalmologist population are changing, especially w.r.t age and gender.

Of course, delegate attendance varies depending on the time slot provided for the presentation, day of the presentation, and occurrence of some prime events at the same time as the presentation and many other difficult to quantify factors. Data about delegate attendance for all speakers must be shared between organizers of conferences along with the quantifiable variables. A pre-conference survey performed sufficiently early about the topics of audience preference may also help to reduce the number of halls and monetary wastage.

Yet, I feel that the real beneficiaries are the speakers at these events who have enriched themselves by preparing extensively for the event. Despite poor attendance in the halls, there is no decline in the number of Instruction Courses submitted or a dearth of speakers. Understandably, this trend will die its natural death in the mega events, but academic participation in niche events will rise in the coming years especially in the subspecialties of Ophthalmology. Even in the niche events, niche(r) areas will be identified. Already, single disease-centric CMEs (Continuation of Medical Education) are gaining attention. The demand for skilled and trained professionals in any field, especially Ophthalmology, is always high. Obviously, these niche areas should be focused on skill development to ensure efficiency.[2]

Skill transfer sessions are in great demand. The participation of trade in these sessions makes it more practical. Simulation training sessions offer ophthalmologists to get hands-on experience before practicing them in real patients. These personalized sessions provide the opportunity to practice skills and can effect change in professional practice and, on occasion, health care outcomes. Interactive CMEs that enhance participant activity, for example, case-based panel discussions, enable honing the practical skills in managing a patient. Based on a small number of well-conducted trials, didactic sessions do not appear to be effective in changing physician performance.[3]

While we were witnessing audience dissatisfaction at being lectured down, the attendance was at its peak during the quiz programs. The relative anonymity combined with the relative recognition (even though it seems an oxymoron), the great prizes, and the fun of participation makes it a much-awaited event. Perhaps, each of the subspecialties of Ophthalmology should come up with its own quiz session which will enliven conferences for a few years.

Paradoxically, even though there is a lament on the decline in attendance in halls, the number of attendees at a conference

is the same or increasing. Many are seen hanging out in the corridors, at the food counters or the trade exhibitions. For them, the conference is an excellent opportunity for networking. Bhattacharya calls them the "outstanding delegates" and those attending the trade stalls as the "stalwarts." Though there are multiple WhatsApp groups and Facebook or other social media accounts for extracting information from experts, the advantages of face-to-face interactions cannot be negated.[4]

Nowadays, most of the mega conferences are carnivalesque events that ophthalmologists attend to relieve the stress of day-to-day work in a five-star atmosphere with celebrations organized by very experienced event managers at scenic locations. The banquets, the spectacular inaugural events, and the sociocultural extravaganzas in the evenings are the icings on the cake. At times, they seem like sham academic events of practicing ophthalmologists. Soon we shall have "predator conferences," arranging systems for procuring credit points. Quality monitoring bodies must be extra vigilant by implementing strong guidelines to prevent this state of deterioration.

There are many fixed programs in an annual conference. The General Body or the Executive Committee of the organizing bodies should make steps to prune the redundant ones to make the conference compact. At the state level, the annual conferences of the District Ophthalmic Clubs should be made once in two years, but the monthly meetings must be held regularly.

Just like history, trends in Ophthalmic conferences will repeat themselves. It is for us to learn from history so that mistakes are not repeated, and new trends are created.

Smita Narayanan

Regional Institute of Ophthalmology, Thiruvananthapuram, Kerala, India

Address for correspondence: Dr. Smita Narayanan, 3B, Condor Marigold, Near DPI, Thycaud P. O, Thiruvananthapuram - 695 014, Kerala, India.
E-mail: drsmita.narendranath@gmail.com

REFERENCES

1. Loannidis JP. Are medical conferences useful? And for whom? JAMA 2012;307:1257-8.
2. Pandey SK, Sharma V. Are ophthalmic conferences losing their relevance and how to reverse this trend? Indian J Ophthalmol 2019;67:440-1.
3. Davis D, O'Brien MA, Freemantle N, Wolf FM, Mazmanian P, Taylor-Vaisey A. Impact of formal continuing medical education: Do conferences, workshops, rounds, and other traditional continuing education activities change physician behavior or health care outcomes? JAMA 1999;282:867-74.
4. Bhattacharya S. Was attending the conference worth value for money? Indian J Plast Surg 2014;47:1-3.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Submitted: 21-Jun-2023 **Accepted:** 27-Jun-2023 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	Quick Response Code
DOI: 10.4103/kjo.kjo_82_23	

How to cite this article: Narayanan S. Ophthalmic conferences: Time for change? Kerala J Ophthalmol 2023;35:121-2.

IOL opacification: My perspective



Millions of cataract surgeries are being performed worldwide. The final visual acuity after cataract surgery depends on different factors including surgical technique, possible complications, and the material of the intraocular lens (IOL) used. One of the infrequent and late complications affecting patients' quality of vision is IOL opacification. IOL opacification is a complication solely due to the biomaterial of the intraocular lens. The main IOL materials used are hydrophilic and hydrophobic acrylic, PMMA, and silicone.[1] The type of IOL opacification depends on the material of the IOL. Calcification of IOLs develops more often in hydrophilic acrylic lenses while IOL glistenings are seen more in hydrophobic acrylic lenses. IOL calcification causes significant visual disability while IOL glistenings affect visual quality by causing significant glare.[2] Snowflake degenerations are seen as intra-optic spherical lesions in PMMA material lenses.[1]

Glistenings are due to small fluid-filled vacuoles in the IOL material. It can be found in all IOL materials but predominantly in hydrophobic acrylic lenses. In a study conducted by Yildirim *et al.*[3] glistening was highest in the central part of the optic in Acrysof IQ lenses compared to Eyecryl Plus ASHFY600. Colin *et al.*[4] reported the formation of glistenings in 86.5% of implanted AcrySof SN60WF IOLs. The new Clareon CNA0T0 exhibited among the lowest levels of surface haze and roughness, nano glistenings, and glistenings compared with other commercially available hydrophobic acrylic IOLs (Tecnis ZCB00 and Tecnis OptiBlue ZCB00V, Eternity W-60, enVista MX60, and Vivinex XY1).[5] Glistening affects the quality of vision mainly by inducing glare rather than lowering visual acuity or contrast sensitivity.[1]

Calcification occurs as a result of accumulation of the calcium phosphate deposits in various IOLs. Calcification can affect the central optic or different parts of the IOL. It can look similar to posterior capsular opacification and hence it is often misdiagnosed and even treated with NdYAG laser in many patients. IOL exchange is the only available treatment option in such patients to restore vision. Studies report IOL calcification more commonly in hydrophilic acrylic IOLs.[6] Recent reports document an increase in centrally located IOL calcification following DSAEK, DMEK, or PPV following intraocular injection of gas or air. Most cases of IOL calcification result in significant visual disability which eventually might require explanation. Maceda *et al*. report the explantation of seventy-one opacified hydrophilic acrylic intraocular lenses by the same manufacturer implanted between 2009 to 2012 as they developed late calcification with significant visual loss after routine cataract surgery.[7]

To better understand the prevalence, types, and management strategies for IOL opacification, the KJO conducted an online survey using Google Forms in June 2023. The questions were designed to address the experiences of Ophthalmologists regarding IOL opacification.

97.2 percent of the participants have seen cases of opacified IOLs. More than 50 percent of participants have seen more than 4 cases of opacified IOL in their practice. From the survey, most of the IOLs were implanted between 2012 to 2016 and 60 percent of opacifications were documented after 2-5 years of cataract surgery. Opacifications were maximum noted with hydrophilic acrylic lenses (50.8%). Other lens materials with opacification include hydrophobic acrylic IOL (23.1%), PMMA (13.8%), and silicone IOL (<1%). 72.5% of opacified IOLs caused significant vision loss [Figure 1]. 55 percent of participants managed this complication with the IOL exchange. Most of the cases were replaced with a

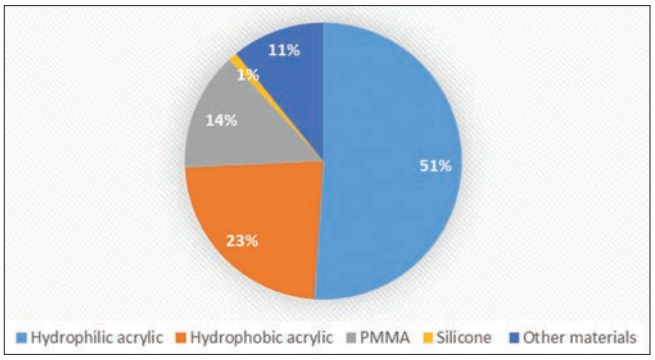


Figure 1: Material of opacified intraocular lenses

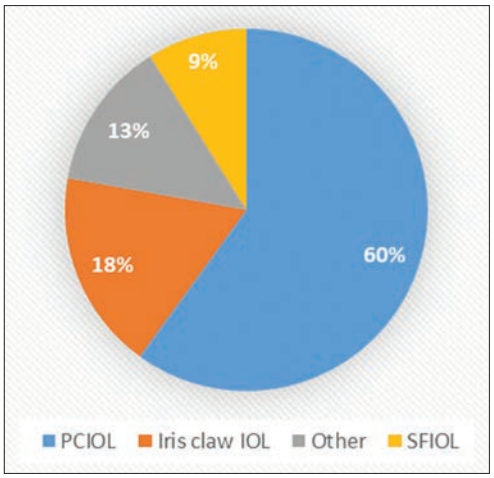


Figure 2: Type of secondary intraocular lens used in IOL exchange

PCIOL while 17 percent used iris claw IOL and 8.9 percent used SFIOL [Figure 2]. Opacified IOL was in the bag in most of the cases. In situations where it was replaced by a PCIOL, 28.3% responded that they could keep the IOL in the bag. Perioperative complications noted during IOL exchange include zonular dialysis (28.8%), PC rent (19.6%), and corneal decompensation (2.1%). 90.7 percent of the participants confirmed that the best corrected visual acuity post-IOL exchange obtained was between 6/18 to 6/9.

Like other respondents in the study, I have also experienced IOL opacification, mainly in hydrophilic lenses. Out of the nine lenses I explanted, 8 were hydrophilic lenses from a particular manufacturer. I could save the posterior capsule in only 5 out of the 9 cases. In all these cases, the new lens was placed in the sulcus since the bag could not be opened. All four cases which had a loss of posterior capsule were replaced with iris claw lenses. I also had one case of an open PC, because she had undergone Nd YAG capsulotomy from elsewhere.

This KJO survey throws light on a not so common, but very important late complication of IOL implantation. Hopefully, this Editorial will stir interest and research in the management of opacified IOLs. Let me thank all the Ophthalmic Surgeons who took the time to respond to this survey and share their experience.

S. J. Saikumar

Medical Superintendent and Head of Cataract and Glaucoma Services, Giridhar Eye Institute, Kochi, Kerala, India

Address for correspondence: Dr. S. J. Saikumar, Medical Superintendent and Head of Cataract and Glaucoma Services, Giridhar Eye Institute, Kochi, Kerala, India.
E-mail: saikumarsj@yahoo.com

REFERENCES

1. Bellucci R. An introduction to intraocular lenses: Material, optics, haptics, design and aberration. ESASO Course Series. Cataract. Vol. 3. Basel: Karger; 2013. p. 38-55.
2. Grzybowski A, Markeviciute A, Zemaitiene R. A narrative review of intraocular lens opacifications: Update 2020. Ann Transl Med 2020;8:1547.
3. Yildirim TM, Fang H, Schickhardt SK, Wang Q, Merz PR, Auffarth GU. Glistening formation in a new hydrophobic acrylic intraocular lens. BMC Ophthalmol 2020;20:186.
4. Colin J, Praud D, Touboul D, Schweitzer C. Incidence of glistenings with the latest generation of yellow-tinted hydrophobic acrylic intraocular lenses. J Cataract Refract Surg 2012;38:1140-6.
5. Werner L, Thatthamla I, Ong M, Schatz H, Garcia-Gonzalez M, Gros-Otero J, *et al*. Evaluation of clarity characteristics in a new hydrophobic acrylic IOL in comparison to commercially available IOLs. J Cataract Refract Surg 2019;45:1490-7.
6. Barra D, Werner L, Costa JL, Morris C, Ribeiro T, Ventura BV, *et al*. Light scattering and light transmittance in a series of calcified single-piece hydrophilic acrylic intraocular lenses of the same design. J Cataract Refract Surg 2014;40:121-8.
7. Gurabardhi M, Häberle H, Aurich H, Werner L, Pham DT. Serial intraocular lens opacifications of different designs from the same manufacturer: Clinical and light microscopic results of 71 explant cases. J Cataract Refract Surg 2018;44:1326-32.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Submitted: 18-Jul-2023 **Revised:** 23-Jul-2023 **Accepted:** 28-Jul-2023 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	Quick Response Code
DOI: 10.4103/kjo.kjo_94_23	

How to cite this article: Saikumar SJ. IOL opacification: My perspective. Kerala J Ophthalmol 2023;35:123-4.

Exploring the therapeutic potential of stem cells in glaucoma: A promising frontier for vision restoration



Glaucoma is one of the leading causes of irreversible blindness in the world. Pathological features such as thinning of the retinal nerve fiber layer and cupping of the optic nerve head are seen at the optic nerve head.[1] Elevated intraocular pressure (IOP) is a major risk factor for glaucoma, which is associated with inefficient outflow of aqueous humor (AH).[2] In India alone, 12 million people are affected and 1.2 million are blind from glaucoma.[3] The affected individuals are expected to reach 111.8 million worldwide in 2040.[4]

Although IOP management is important, retinal ganglion cells (RGCs) are the primary cause of vision loss associated with glaucoma because their axons generate the optic nerve. An increased production along with/or decreased outflow of AH results in the development of elevated IOP, which is considered the main reason for enhanced apoptosis of RGCs in glaucoma.[5]

RGCs spontaneous regeneration is not feasible, hence alleviation of IOP and consequent reduction of RGCs loss are currently the main approaches in glaucoma prevention and therapy.[6]

Prevention of the disease is the best approach for glaucoma.[7] The significant retinal nerve fiber damage and cell death in glaucoma before the patient experiences detectable visual field loss is making early detection and treatment challenging.

The trabecular meshwork (TM), ciliary muscle, and Schlemm's canal inner wall cells play a role in the natural process of IOP homeostasis, which results in variations in outflow resistance as a result of pressure fluctuations.[8] During aging, TM cells experience various molecular and morphological changes that cause a steady decline in the number of cells and an increase in IOP,[9] indicating that TM cells may be crucial in preserving a normal IOP and preventing glaucoma. The current practices in the therapeutic options offered for glaucoma include medical and surgical methods to reduce pressure, which controls the RCG death and prevents or slows further progression.

Yet, none of the current medications specifically target TM. Several studies are now focussing on stem cell therapy for regenerating functional TM thereby reducing IOP, and RGC apoptosis, and ultimately preventing vision loss.[10,11]

Thus, cell-based functional restoration of TM in glaucoma-affected eyes is a potentially viable treatment. According to numerous studies, the cells in TM still possess adult stem cell characteristics. It is uncertain if trabecular meshwork-derived stem cells (TMSCs) can be proliferated without losing their phenotype and, if so, whether they can be exploited for glaucoma regeneration therapy.

STEM CELLS AS VISION-RESTORING ALLIES

Stem cells are immature, uncommitted cell types with the capacity to self-renew endlessly through symmetric cell division and undergo asymmetric cell division, producing another stem cell and a daughter cell that can differentiate into a variety of mature cell types. Embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) are two examples of pluripotent stem cells that can produce all cell types in the developing and adult body, whereas multipotent somatic stem cells are dedicated to a particular developmental lineage.[12] Stem cells commit to a certain lineage and differentiate into progenitor cells during differentiation. These cells eventually develop into adult cells.[13]

Stem cells can be obtained from various sources, such as ESCs, which arise from the inner mass of the blastocyst after fertilization in humans. Adult tissue-derived stem cells offer an alternative for the development of cell-based therapies, which circumvents the ethical controversies surrounding fetal and embryonic tissue.[14] Stem cells have shown promising potential in the field of glaucoma

research and treatment as they have the potential to regenerate damaged tissues in the eye.[15] Certain stem cells which have shown promising effects in regulating IOP are discussed below:

TMSCs

There have been several potential cell-based therapeutics for TM regeneration in glaucoma therapy. The TMSCs have been the first choice as they are tissue-specific stem cells of the TM. Patients with primary open-angle glaucoma (POAG) exhibit a reduction in TM cell content that is more pronounced, with inner tissues being more negatively impacted than outside tissues in the filtering meshwork.[16] As a result, it is important to investigate how stem cells in TM contribute to the preservation of tissue homeostasis. The Schwalbe's line cells, also known as "insert cells," differ morphologically from the remainder of the TM cell. These cells are situated at the "insert" or non-filtering region, also known as Schwalbe's Line, which is the transitional zone between the corneal endothelium and the anterior non-filtering section of the TM.[17] McGowan *et al*.[18] immunostaining investigations revealed that stem cell-like markers, including sex determining region Y-box 2 (SOX2), octamer-binding transcription factor ¾ (OCT ¾), and others, were present in the region between the TM and corneal endothelium, indicating that these stem cells could replenish either the TM or the corneal endothelium. These stem cells are supposed to repopulate the TM when damage occurs. But why these cells do not repopulate the TM in old age and glaucoma when TM cell numbers decline is still unknown.

When human TMSCs were administered to healthy mice's anterior chambers, they found their way to the TM and developed into TM cells. They were discovered to be viable for at least 4 months, and neither had any inflammatory response nor an elevation in IOP.[19] A possible explanation for why xenotransplantation did not result in immune rejection or inflammation is because TMSCs share the immunosuppressive qualities of the MSCs.[20]

In a different experimental research, TMSCs repaired the TM cells, controlling the IOP. The TM was likewise rebuilt, fibrosis was avoided, and the IOP was maintained following laser photocoagulation compared to the fibroblast injection (control) group.[21] These observations, albeit in mouse models, suggest that TMSC transplantation may be a potential strategy to lower IOP, boost outflow capability, and shield against vision loss in the treatment of glaucoma. In addition, even after eight years of cryopreservation, TMSC still exhibited stem cell characteristics.[22]

Other Stem Cell Population Involved in TM Regeneration

Due to a lack of TM stem cell production or the presence of mutant or damaged cells in glaucomatous patients, other stem cell types, such as bone marrow-derived stem cells BMDSCs, adipose-derived stem cells (ADSCs), and iPSCs, have been investigated as potential replacements for TMSC harvesting for TM regeneration.

iPSCs

iPSCs can be generated from skin or blood cells through reprogramming using transcription factors such as SOX2, Octamer-binding transcription factor 4 (Oct4), Krüppel-like factor 4 (KLF4), etc.[23] By differentiating these iPSCs into TM cells in a laboratory setting, researchers can gain insights into the mechanisms underlying TM dysfunction and glaucoma pathology. In an *ex vivo* perfused human organ culture model, the generated TM cells from iPSC completely repaired IOP homeostatic function.[24] After 12 weeks of injecting iPSC-TM into the anterior chamber of 6-month-old Tg-MYOCY437H mice, older animals who had received iPSC-TM transplants had higher AH outflow capacity, lower IOP, and more cellularity in their TM.[25]

BMDSCs

BMDCs refer to a group of cells that originate from the bone marrow. BMDCs are known to contain different types of stem cells, such as hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs).[26] Researchers have explored the use of BMDCs, particularly MSCs, for potential therapeutic strategies in glaucoma and trabecular meshwork dysfunction. For example, 1 month after the injection of BMMSCs, into the anterior chamber of laser-photocoagulation mice, the MSCs moved to the laser-treated area and repaired the TM structure. In addiion, the infusion of MSC-conditioned media produced under low-oxygen conditions significantly decreased IOP.[27] In a study by Roubeix *et al*.[28] intracameral injection of MSCs into the glaucoma-like ocular hypertension model's eyes dramatically lowered IOP compared to the controls. MSCs were discovered at the iridocorneal angle, corneal endothelium, and TM 24 days after the implantation. In addition, ocular hypertensive eyes treated with MSCs had greater peripheral RGC density than untreated eyes.

ADSCs

ADSCs have gained significant attention in regenerative medicine due to their abundance, ease of isolation, and potential for differentiation into various cell types.[29] The delivery of ADSCs to the TM within 15 minutes of exposure to the magnetic field following injection into the anterior chamber of pig eyes raises the possibility that these cells can also be employed for TM regeneration.[30] After being injected into naive mice, the ADSC was homed to the TM cells and enhanced the IOP, outflow facility, and ECM.[11]

Exosomes

It is now widely accepted that a major therapeutic effect of stem cells is due to their secretion of paracrine factors like exosomes[31] [Figure 1]. Exosomes are one of the widely used therapeutic agents in cell-free therapy.[32] Exosomes are formed when the intraluminal vesicles formed by the limiting membrane of multivesicular bodies invaginate inward to release into the extracellular milieu.[33] Exosomes from nonpigmented ciliary epithelium controlled wingless-related integration site (Wnt) signaling in TM cells, indicating cell-to-cell communication.[34] IOP is regulated by Wnt signaling, which is one of the main suspects in glaucoma.[35] Human TM-derived exosome proteomic analysis revealed the presence of the glaucoma-causing protein Myocilin (MYOC), indicating that exosomes have a role in controlling IOP.[36] Although several studies have been conducted on the therapeutic effects of stem cell-derived exosomes and RGCs, there are limited studies on TMSCs or TMSC-derived exosomes.

CLINICAL TRIALS

Clinical trials play a crucial role in advancing our understanding of glaucoma, developing new treatment options, and improving patient outcomes. In a clinical trial from Brazil (#NCT02330978, Phase I completed), the effects of autologous BMMSCs have been evaluated in the patients' eyes with bilateral blindness caused due to glaucoma. In another trial (#NCT05147701, under Phase I), cultured allogeneic adult umbilical cord-derived MSCs will be analyzed in ophthalmic diseases. This shows that stem cell research has gained significant attention in ophthalmology, but the studies of TMSCs in glaucoma are still relatively limited. This may be due to several reasons, such as the complexity of the TM's cellular environment and the challenges associated with studying stem cells in this specific context.

CONCLUSION

In conclusion, stem cells play a crucial role in trabecular meshwork regeneration in glaucoma. MSCs, ADSCs, iPSCs, and TMSCs have shown promising results in preclinical and clinical studies for their ability to regenerate the trabecular meshwork and improve IOP. In addition, the release of exosomes from these stem cells can also contribute to trabecular meshwork regeneration through their ability to transfer functional and regulatory molecules to target cells.

While the use of TM-derived stem cells for glaucoma treatment is a promising and rapidly evolving field, further

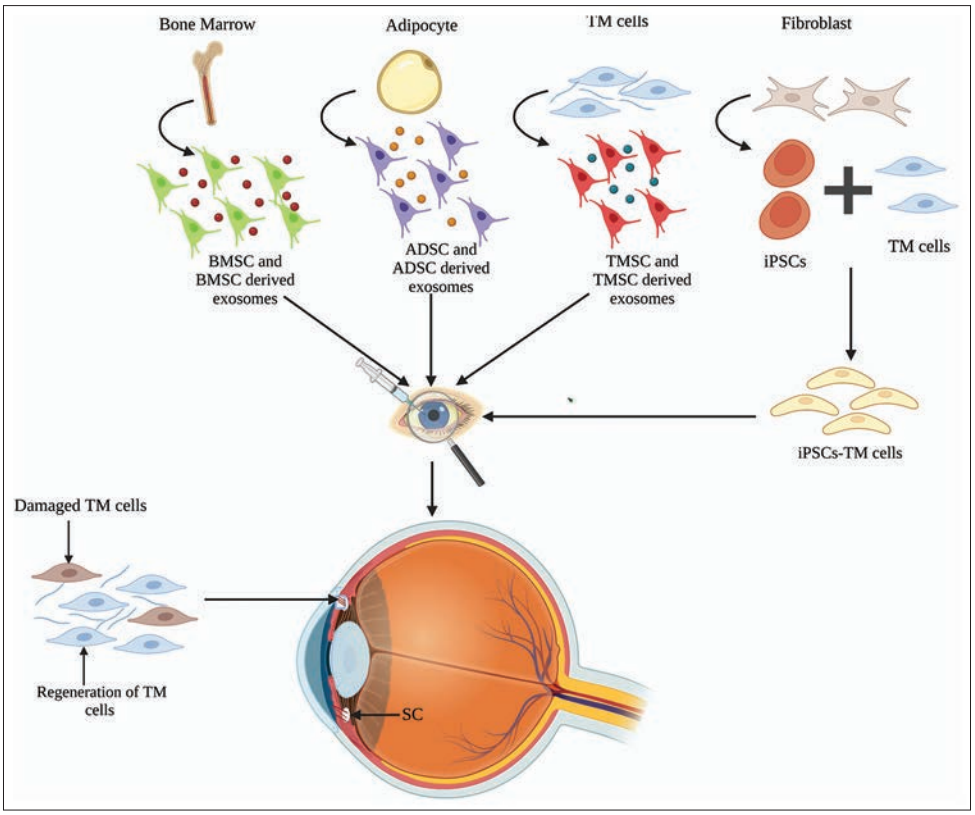


Figure 1: Regeneration of the trabecular meshwork via stem cells and exosomes. Bone marrow stem cell (BMSC), adipose-derived stem cells (ADSC), trabecular meshwork stem cells (TMSC) derived exosomes, induced pluripotent stem cells-trabecular meshwork cells (iPSC-TM) can regenerate the damaged trabecular meshwork

research is necessary to fully understand their therapeutic potential and establish their clinical viability. Continuous advancements in stem cell technology and rigorous scientific investigations will contribute to the development of innovative treatments for glaucoma, offering hope for improved outcomes and quality of life for patients with this sight-threatening condition.

Suneeta Dubey[1], Nisha Sinha[2]

[1]Department of Glaucoma, [2]Eicher-Shroff Center for Stem Cell Research, Dr. Shroff's Charity Eye Hospital, New Delhi, India

Address for correspondence: Dr. Suneeta Dubey, Department of Glaucoma, Dr. Shroff's Charity Eye Hospital, Daryaganj, New Delhi – 110 002, India.
E-mail: dubeysuneeta@hotmail.com

REFERENCES

1. Quigley HA. Open-angle glaucoma. N Engl J Med 1993;328:1097-106.
2. Acott TS, Keller KE, Kelley MJ. Role of proteoglycans in the trabecular meshwork. In the curated reference collection in neuroscience and biobehavioral psychology. Elsevier Science Ltd; 2016. p. 170-8. doi: 10.1016/B978-0-12-809324-5.01518-2.
3. Senjam SS. Glaucoma blindness-A rapidly emerging non-communicable ocular disease in India: Addressing the issue with advocacy. J Family Med Prim Care 2020;9:2200-6.
4. Tham Y-C, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: A systematic review and meta-analysis. Ophthalmology 2014;121:2081-90.
5. Almasieh M, Wilson AM, Morquette B, Cueva Vargas JL, Di Polo A. The molecular basis of retinal ganglion cell death in glaucoma. Prog Retin Eye Res 2012;31:152-81.
6. Daliri K, Ljubimov AV, Hekmatimoghaddam S. Glaucoma, stem cells, and gene therapy: Where are we now? Int J Stem Cells 2017;10:119-28.
7. Xu ZR, Jiang FG, Chen F. Effects of abnormal optineurin expression on the survival of the rat retinal ganglion cell line RGC-5. Genet Mol Res 2015;14:9171-80.
8. Du Y, Roh DS, Mann MM, Funderburgh ML, Funderburgh JL, Schuman JS. Multipotent stem cells from trabecular meshwork become phagocytic TM cells. Invest Ophthalmol Vis Sci 2012;53:1566-75.
9. Sundaresan Y, Veerappan M, Ramasamy KS, Chidambaranathan GP. Identification, quantification and age-related changes of human trabecular meshwork stem cells. Eye Vis 2019;6:31.
10. Xiong S, Xu Y, Wang Y, Kumar A, Peters DM, Du Y. α5β1 Integrin promotes anchoring and integration of transplanted stem cells to the trabecular meshwork in the eye for regeneration. Stem Cells Dev 2020;29:290-300.
11. Zhou Y, Xia X, Yang E, Wang Y, Marra KG, Ethier CR, *et al*. Adipose-derived stem cells integrate into trabecular meshwork with glaucoma treatment potential. Faseb J 2020;34:7160-77.
12. Johnson TV, Bull ND, Martin KR. Stem cell therapy for glaucoma: Possibilities and practicalities. Expert Rev Ophthalmol 2011;6:165-74.
13. Enver T, Pera M, Peterson C, Andrews PW. Stem cell states, fates, and the rules of attraction. Cell Stem Cell 2009;4:387-97.
14. Zakrzewski W, Dobrzyński M, Szymonowicz M, Rybak Z. Stem cells: Past, present, and future. Stem Cell Res Ther 2019;10:68.
15. Nicoară SD, Brie I, Jurj A, Soriţău O. The future of stem cells and their derivates in the treatment of glaucoma. A critical point of view. Int J Mol Sci 2021;22:11077. doi: 10.3390/ijms222011077.
16. Alvarado J, Murphy C, Juster R. Trabecular meshwork cellularity in primary open-angle glaucoma and nonglaucomatous normals. Ophthalmology 1984;91:564-79.
17. Raviola G. Schwalbe line's cells: A new cell type in the trabecular meshwork of Macaca mulatta. Invest Ophthalmol Vis Sci 1982;22:45-56.
18. McGowan SL, Edelhauser HF, Pfister RR, Whikehart DR. Stem cell markers in the human posterior limbus and corneal endothelium of unwounded and wounded corneas. Mol Vis 2007;13:1984-2000.
19. Du Y, Yun H, Yang E, Schuman JS. Stem cells from trabecular meshwork home to TM tissue *in vivo*. Invest Ophthalmol Vis Sci 2013;54:1450-9.
20. Coulon SJ, Schuman JS, Du Y, Bahrani Fard MR, Ethier CR, Stamer WD. A novel glaucoma approach: Stem cell regeneration of the trabecular meshwork. Prog Retin Eye Res 2022;90:101063. doi: 10.1016/j.preteyeres. 2022.101063.
21. Yun H, Wang Y, Zhou Y, Kumar A, Wang K, Sun M, *et al*. Author correction: Human stem cells home to and repair laser-damaged trabecular meshwork in a mouse model. Commun Biol 2021;4:456.
22. Kumar A, Xu Y, Du Y. Stem cells from human trabecular meshwork hold the potential to develop into ocular and non-ocular lineages after long-term storage. Stem Cells Dev 2020;29:49-61.
23. Medvedev SP, Shevchenko AI, Zakian SM. Induced pluripotent stem cells: Problems and advantages when applying them in regenerative medicine. Acta Naturae 2010;2:18-28.
24. Abu-Hassan DW, Li X, Ryan EI, Acott TS, Kelley MJ. Induced pluripotent stem cells restore function in a human cell loss model of open-angle glaucoma. Stem Cells 2015;33:751-61.
25. Zhu W, Jain A, Gramlich OW, Tucker BA, Sheffield VC, Kuehn MH. Restoration of aqueous humor outflow following transplantation of iPSC-Derived trabecular meshwork cells in a transgenic mouse model of glaucoma. Invest Ophthalmol Vis Sci 2017;58:2054-62.
26. Kemp KC, Hows J, Donaldson C. Bone marrow-derived mesenchymal stem cells. Leuk Lymphoma 2005;46:1531-44.
27. Manuguerra-Gagné R, Boulos PR, Ammar A, Leblond FA, Krosl G, Pichette V, *et al*. Transplantation of mesenchymal stem cells promotes tissue regeneration in a glaucoma model through laser-induced paracrine factor secretion and progenitor cell recruitment. Stem Cells 2013;31:1136-48.
28. Roubeix C, Godefroy D, Mias C, Sapienza A, Riancho L, Degardin J, *et al*. Intraocular pressure reduction and neuroprotection conferred by bone marrow-derived mesenchymal stem cells in an animal model of glaucoma. Stem Cell Res Ther 2015;6:177.
29. Wankhade UD, Shen M, Kolhe R, Fulzele S. Advances in adipose-derived stem cells isolation, characterization, and application in regenerative tissue engineering. Stem Cells Int 2016;2016:3206807. doi: 10.1155/2016/3206807.
30. Snider EJ, Kubelick KP, Tweed K, Kim RK, Li Y, Gao K, *et al*. Improving stem cell delivery to the trabecular meshwork using magnetic nanoparticles. Sci Rep 2018;8:12251.
31. Han Y, Yang J, Fang J, Zhou Y, Candi E, Wang J, *et al*. The secretion profile of mesenchymal stem cells and potential applications in treating human diseases. Signal Transduct Target Ther 2022;7:92.
32. Rad LM, Yumashev AV, Hussen BM, Jamad HH, Ghafouri-Fard S, Taheri M, *et al*. Therapeutic potential of microvesicles in cell therapy and regenerative medicine of ocular diseases with an especial focus on mesenchymal stem cells-derived microvesicles. Front Genet 2022;13:847679. doi: 10.3389/fgene. 2022.847679.
33. Sinha N, Kumar V, Puri V, Nada R, Rastogi A, Jha V, *et al*. Urinary exosomes: Potential biomarkers for diabetic nephropathy. Nephrology (Carlton) 2020;25:881-7.
34. Lerner N, Avissar S, Beit-Yannai E. Extracellular vesicles mediate signaling between the aqueous humor producing and draining cells in the ocular system. PLoS One 2017;12:e0171153. doi: 10.1371/journal.pone. 0171153.
35. Villarreal G Jr, Chatterjee A, Oh SS, Oh DJ, Kang MH, Rhee DJ. Canonical wnt signaling regulates extracellular matrix expression in

the trabecular meshwork. Invest Ophthalmol Vis Sci 2014;55:7433-40.
36. Stamer WD, Hoffman EA, Luther JM, Hachey DL, Schey KL. Protein profile of exosomes from trabecular meshwork cells. J Proteomics 2011;74:796-804.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Submitted: 17-Jul-2023 **Revised:** 20-Jul-2023 **Accepted:** 28-Jul-2023 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	**Quick Response Code**
DOI: 10.4103/kjo.kjo_93_23	

How to cite this article: Dubey S, Sinha N. Exploring the therapeutic potential of stem cells in glaucoma: A promising frontier for vision restoration. Kerala J Ophthalmol 2023;35:125-9.

Review Article

Ophthalmic prostaglandin analogs revisited - A systematic review of commonly used formulations

ABSTRACT

Aim: To systematically review the randomized control trials (RCTs) of the various prostaglandin(PG) analogues, comparing the effectiveness in treating glaucomas, safety and adverse effects of the individual agents. **Methods:** Articles were searchedusing the following key words "PG analogues", "Latanoprost", " Bimatoprost", "Travoprost", " Tafluprost", "Unoprostone", "ophthalmology", "randomized controlled trial", either singly or variably combined. Databases searched included Pubmed, Embase, Cochrane library, and Science direct. The search strategy was to identify randomized control trials (RCTs), either singly or variably combined. **Results:** 24 Randomised control trials that had evaluated the efficacy and adverse effects of different PG analogue agents were selected and were used in this review Average JADAD value of the researches was found to be 2.83. Bimatoprost was found to be the most effective agent in IOP lowering efficacy but it had the maximal incidence of local adverse effects. Latanoprost, Travoprost and Tafluprost had similar efficacy. Latanoprost had the best tolerability. Unoprostone had weaker antiglaucoma action, compared to the other agents. **Conclusions:** Bimatoprost is probably one of the best antiglaucoma medications available at present. Its tolerability could be improved by using preservative free formulations. Latanoprost is a well tolerated agent with reasonably good antiglaucoma action.

Keywords: Bimatoprost, latanoprost, PG analogs, tafluprost, travoprost, unoprostone

One of the most potent weapons in the armamentarium of the modern glaucoma specialist is the prostaglandin (PG) analogs. Its strong efficacy, combined with once-daily dosing for most of the agents, and minor local adverse effects have made it the most preferred antiglaucoma medication. In 1985, Giuffre first reported the intraocular pressure (IOP) lowering ability of a single dose of PGF 2α tromethamine salt when given to normal volunteers.[1] It needed 11 years of research to bring out the prototype prostaglandin analog, latanoprost for commercial use. Ueno developed the first commercially available PG analog, unoprostone in Japan in 1994. The duration of action is lesser than the other PG agonists, mandating twice-daily dosing unlike the other PG analogs, and so it is rarely used nowadays.[2] Latanoprost 0.005% was launched in 1996 as a single dose antiglaucoma medication and is probably one of the most effective medications in the management of open-angle glaucomas (OAGs) and ocular hypertension.[3] Another PG analog, bimatoprost 0.03% was approved for use in the US in the year 2001. Similarly, travoprost 0.004% was approved by the USFDA in March 2001 for the treatment of raised IOP in patients with OAG and ocular hypertension.[4] Tafluprost 0.0015%, a fluoroprostaglandin receptor analog introduced in 2008, was the first PG analog to be available in preservative free form, which is an attractive option to reduce ocular surface problems.[5] The attractive features of PG analogs are their efficacy, single-day dosing, and the relative absence of adverse effects, especially systemic ones. Ocular hyperemia is one of the commonest adverse effects.

The most popular agents are latanoprost, bimatoprost, and travoprost, and there have been numerous studies comparing

Kaberi Biswas Feroze

Department of Ophthalmology, Al Azhar Medical College, Thodupuzha, India

Address for correspondence: Dr. Kaberi Biswas Feroze, Department of Ophthalmology, Al Azhar Medical College, Thodupuzha, India.
E-mail: kaberiferoze@gmail.com

Submitted: 15-Jan-2022 **Revised:** 25-May-2022
Accepted: 22-Jul-2022 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	Quick Response Code
DOI: 10.4103/kjo.kjo_5_22	

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Feroze KB. Ophthalmic prostaglandin analogs revisited - A systematic review of commonly used formulations. Kerala J Ophthalmol 2023;35:130-8.

© 2023 Kerala Journal of Ophthalmology | Published by Wolters Kluwer - Medknow

these agents, however with variable results.[6] Some studies show that bimatoprost is the most potent IOP lowering agent among the PG analogs,[7,8] whereas others have equivocal results.[9] Regarding the adverse effects, bimatoprost is considered to be the agent most frequently associated with ocular hyperemia.[10] Other PG analogs include tafluprost and unoprostone. Systematic reviews on these agents are very few.

This review was conducted to systematically review the randomized control trials (RCTs) of the various PG analogs, comparing the effectiveness in treating glaucomas, safety, and adverse effects of the individual agents.

MATERIALS AND METHODS

Search strategy

The search strategy included the following keywords "PG analogues," "Latanoprost," "Bimatoprost," "Travoprost," " Tafluprost," "Unoprostone," "ophthalmology," "randomized controlled trial," either singly or variably combined. Databases searched included PubMed, Embase, Cochrane Library, Saudi digital library, and Science Direct. The search strategy was to identify RCTs, either singly or variably combined.

Inclusion and exclusion criteria

Researches were included in the study if it fulfilled all the following inclusion criteria:

a. Studies involved comparison of topical prostaglandin analogs
b. Studies were randomized
c. Treatment effects of prostaglandin analogs were measured.

Exclusion criteria included the following:

a. Studies not comparing the action of different PG groups
b. Studies involving PG combined with antiglaucoma medication of another group
c. Articles that were not an RCT
d. Treatment effects of PG analogs were not measured
e. Articles in which full text in English could not be obtained.

Data selection

All the obtained data were screened according to the inclusion/exclusion criteria. Only RCTs were included in this study. Seventy-three RCTs were retrieved, and after applying

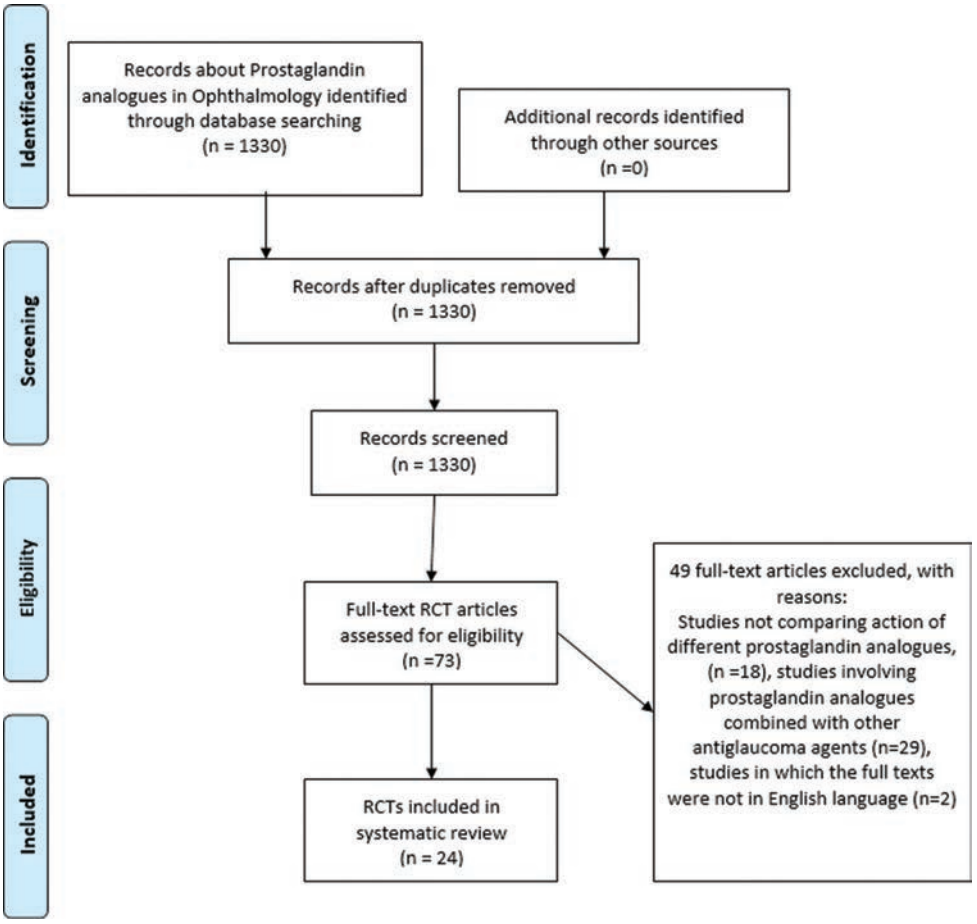


Figure 1: Decision tree flow diagram (adapted from: http://prisma-statement.org/prismastatement/flowdiagram.aspx)

Table 1: A comparison of different prostaglandin preparations

RCT/Ref	Study group	Study method	No. of subjects	Intervention	Control	Treatment duration	Time points of evaluations	Result
El Hajj Moussa *et al*.[12]	Newly diagnosed primary open-angle glaucoma (POAG) patients	Randomized control trial	32 patients	Tafluprost	Other PG analogs	6 months	1, 3, and 6 months	All the drugs were found to be equally effective in controlling IOP, but bimatoprost was found to provide lower IOPs than the other agents. Mean IOP reductions for bimatoprost were about 39% at 3 months and 40.5% at 6 months. Travoprost- 28.5% (3 months) and 31% (6 M). Tafluprost- 33% (3M) and 28% (6 M). Latanoprost -31%(3M) and 29.5% (6M). Latanoprost was found to be least tolerated according to OSDI scores
Ge *et al*.[13]	POAG or ocular hypertension	RCT	246	Tafluprost 0.0015% (122 subjects)	Latanoprost 0.005% (124 subjects)	4 weeks	2 weeks, 4 weeks	The efficacy and safety of tafluprost were found to be non-inferior to latanoprost in POAG and ocular hypertension. Percentage change in IOP was slightly higher for tafluprost compared to latanoprost. The percentage change in IOP at the end of the treatment period was 37.2% ± 13.4% in the tafluprost group and 35.7% ± 13.0% in the latanoprost group. The incidence of adverse reactions was 31.7% in the tafluprost group and 20.8% in the latanoprost group
Konstas *et al*.[14]	POAG or Ocular hypertension	RCT	38	Tafluprost once daily×3 months, then cross over to latanoprost once daily×3 months	Latanoprost once daily×3 months, then cross over to tafluprost once daily×3 months	6 months	3 months, 6 months	Tafluprost showed similar 24 h IOP control to latanoprost. Latanoprost demonstrated significantly lower IOP trough and tafluprost showed significantly lower IOP fluctuations. The reduction in mean IOP was 29.9% for latanoprost and 28.5% for tafluprost. The adverse effect profile was almost similar.
Shin *et al*.[15]	Patients with normal-tension glaucoma (NTG)	Randomized cross over study	50	Tafluprost once daily×2 months, then travoprost once daily×2 months	Travoprost once daily×2 months, then tafluprost once daily×2 months	4 months	2 months, 4 months	Both tafluprost and travoprost were effective in lowering IOP and increasing mean ocular perfusion pressure throughout 24 h in NTG; however, travoprost showed greater IOP reduction in the late afternoon and evening. Also, travoprost was able to achieve a lower mean IOP compared to tafluprost. Mean IOP reduction at 2 months was 14.2% for tafluprost and 19% for travoprost. Adverse effects were similar in both groups.
Park *et al*.[16]	Patients with POAG or NTG	RCT	41	Latanoprost once daily×3 months	Tafluprost once daily×3 months	3 months	1 week, 1 month, 2 months, and 3 months	Both drugs have marked ocular pulse amplitude lowering effect but tafluprost has a better IOP lowering effect than latanoprost. There was a 12.2% IOP lowering noticed with latanoprost and 24.1% with tafluprost at the end of 3 months.
Kawaguchi I *et al*.[17]	Normal healthy subjects	Randomized prospective clinical study	24	Latanoprost 0.005% eye drops once daily in one eye	Travoprost 0.004% in other eye×2 weeks, followed by 6 week washout period, then tafluprost 0.0015%, and bimatoprost 0.3% after 6 week washout	18 weeks	Weeks 1,2, 9,10,17,18	Mean diurnal IOP reduction was similar between latanoprost, travoprost, and tafluprost on days 7 and 14. The mean diurnal IOP reduction with bimatoprost was greater than that with latanoprost. At day 14, the difference in mean IOP between travoprost and latanoprost was about 0.12 mm, between tafluprost and latanoprost 0.13 mm, and between bimatoprost and latanoprost almost 1 mm.
Cantor *et al*.[8]	POAG or ocular hypertension	RCT	157	Travoprost 0.004% once daily	Bimatoprost 0.03% once daily	6 months	Week 1, months 1,3, and 6	Bimatoprost was shown to provide more IOP reduction than travoprost. Bimatoprost produced greater mean IOP reductions at all times. The mean IOP reduction of bimatoprost was 5.3-5.6 mm (23-24%), and travoprost was 4.5-5.4 mm (19-23%). Both agents were well tolerated. However, the incidence of ocular hyperemia was slightly higher with bimatoprost

Contd...

Table 1: Contd...

RCT/Ref	Study group	Study method	No. of subjects	Intervention	Control	Treatment duration	Time points of evaluations	Result
Chander *et al*.[18]	Patients with POAG	RCT	31	Travoprost 0.004% once daily	Bimatoprost 0.03% once daily	12 weeks	Weeks 1,2,4,6,12	Both the PG analogs showed an effective IOP lowering but bimatoprost showed a greater reduction in mean IOP. At the end of 12 weeks, the decrease in mean IOP was 34.94% in the bimatoprost group and 28.02% in the travoprost group. Both agents were well tolerated.
Hepsen *et al*.[19]	Patients with exfoliation syndrome associated with ocular hypertension	Randomized, single masked, and parallel design study	45	Travoprost 0.004%	Latanoprost 0.005% and bimatoprost 0.03%	3 months	Week 1, month 1, and 3	At the end of the 3rd month, the reduction in mean IOP was found to be 33.4% with bimatoprost, 30.6% with latanoprost, and 30.4% with travoprost. All drugs were effective in reducing 24 h IOP but the 24 h range of IOP was lowest with travoprost and was statistically significant at the end of the 3rd month, even though bimatoprost produced lower IOP levels.
Mishra *et al*.[20]	Patient with POAG	RCT	140	Travoprost 0.004% once daily	Latanoprost 0.005% once daily, bimatoprost 0.03% once daily, or timolol gel 0.5% twice daily	3 months	Weeks 2, 6 and 12	At 12 weeks, among the PG anlaogues, bimatoprost was found to be the most effective in reducing IOP, followed by travoprost and latanoprost. Mean IOP reduction at week 12 was found to be 35.9% with bimatoprost, 30.8% with travoprost, 29.9% with latanoprost, and 26.6% with timolol. All the PG analogs were found to be superior to Timolol in IOP reduction. The incidence of conjunctival hyperemia was noted to be more with bimatoprost.
Parrish *et al*.[21]	Open-angle glaucoma or ocular hypertension patient	RCT	410	Travoprost 0.004% once daily	Bimatoprost 0.03% once daily or latanoprost 0.005% once daily	12 weeks	Weeks 6 and 12	All agents had comparable efficacy in lowering IOP, latanoprost having the best tolerability. At week 12, IOP reduction was found to be 7.3±3.2 mm with bimatoprost, 7.0±3.1 with latanoprost, and 6.7±3.2 in the travoprost group. Ocular redness was complained most commonly in the bimatoprost group, followed by the travoprost group.
DuBiner *et al*.[22]	Patients with OAG or ocular hypertension	Randomized, investigator masked cross over study	81	Benzalkonium chloride (BAK)-free travoprost once daily×6 weeks, followed by BAK free bimatoprost×6 weeks	BAK-free bimatoprost once daily×6 weeks, then BAK free travoprost once daily×6 weeks	12 weeks	6 weeks, 12 weeks	BAK-free travoprost was found to be non-inferior to bimatoprost, which was found to have an increased incidence of moderate ocular hyperemia, compared to travoprost. The percentage of IOP reduction for both bimatoprost and travoprost was found to be between 25% and 26%.
Crichton *et al*.[23]	Patients with POAG or ocular hypertension who had received latanoprost monotherapy for at least 1 month	RCT	150	Travoprost 0.004% preserved with sofZia (Alcon Inc.) once daily×12 weeks	Latanoprost 0.005% preserved with 0.02% BAK, or bimatoprost 0.01% preserved with 0.02% BAK×12 weeks	12 weeks	Weeks 1, 4, and 12	There was no significant objective difference in ocular surface tolerability among the three agents
Blondeau *et al*.[24]	POAG/ocular hypertension/ NTG/pigmentary glaucoma/ pseudoexfoliation glaucoma patient who is non-responder to latanoprost after 1 month	RCT	83	Travoprost once daily	Latanoprost once daily or bimatoprost once daily	1 month	1 month	There is no added benefit of another prostaglandin analog in a latanoprost non-responder

Contd...

Table 1: Contd...

RCT/Ref	Study group	Study method	No. of subjects	Intervention	Control	Treatment duration	Time points of evaluations	Result
Noecker *et al.*[7]	Black patients with OAG and ocular hypertension	RCT	94	Travoprost 0.004% once daily×3 months	Bimatoprost 0.03% once daily×3 months	3 months	Months 1, 2, and 3	Both drugs effectively reduced IOP but more patients achieved clinical IOP reduction with bimatoprost. Bimatoprost provided sustained IOP reduction throughout the study period. Mean IOP reduction at 3 months was found to be 27-31% for bimatoprost and 25-28% for travoprost.
Frenkel *et al.*[25]	Patients with glaucoma or ocular hypertension (Jadad - 2)	Randomized clinical comparison	19	Bimatoprost 0.03% one drop	Travoprost 0.004% one drop	36 h	Every 4 h for 36 h	Both bimatoprost and travoprost provide comparable and lasting control of circadian IOP beyond 24 h. This IOP reduction was comparable, both in supine and sitting positions.
Faridi *et al.*[26]	Previously untreated OAG and ocular hypertension patients	RCT	122	Travoprost 0.004% once daily×6 months	Latanoprost 0.005% once daily×6 months/ bimatoprost 0.03% once daily×6 months	6 months	2, 6 months	All three preparations were found to be effective in reducing IOP. In the initial part of the study, bimatoprost was found to be more effective. However, at 6 months, the difference was not statistically significant. (Bimatoprost-35%, travoprost- 30%, latanoprost -29%). Hyperemia was the commonest adverse effect, noted most commonly in the bimatoprost group and least frequently in the latanoprost group.
Gandolfi *et al.*[27]	Patients with glaucoma or ocular hypertension	RCT	222	Latanoprost 0.005% once daily×3 months	Bimatoprost 0.03% once daily×3 months	3 months	1 week, 1 month, 2 months, and 3 months	Both drugs were safe and well-tolerated but bimatoprost achieved lower IOP values than latanoprost. In this study, latanoprost showed a reduction of mean IOP of 29.7%, while bimatoprost showed a mean IOP lowering of 32% at end of 3 months. Conjunctival hyperemia was seen in 36.1% of patients on bimatoprost and 14.2% of patients on latanoprost, and this difference was significant.
Stalmans *et al.*[28]	Patients with ocular hypertension (OHT) or open-angle glaucoma (OAG) with a maximum intraocular pressure (IOP) of 21 mmHg on a preserved prostaglandin monotherapy	Randomized cross over study	67	Latanoprost unit dose preservative-free (LUDPF) once daily×3 months, then bimatoprost unit dose preservative-free (BUDPF) once daily×3 months	Bimatoprost unit dose preservative-free (BUDPF) once daily×3 months, then latanoprost unit dose preservative-free (LUDPF) once daily×3 months	6 months	3 months, 6 months	BUDPF was found to be superior to LUDPF in lowering IOP at 6 months. However, it was noticed that there was no difference in efficacy at 3 months. Both agents show a low frequency of conjunctival hyperemia but it was lower for LUDPF.
Takemoto *et al.*[29]	NTG patients	A prospective, randomized controlled study	48	Latanoprost 0.005% once daily	Isopropyl unoprostone eye drops 0.12% twice daily	3 years	Every 3 months (visual acuity and optic nerve head imaging every 12 months)	No significant differences were noticed between the 2 groups although unoprostone was less effective than latanoprost in lowering IOP. At week 12, the mean IOP reduction was found to be 14±13% in the latanoprost group and 9±10% in the unoprostone group.
Aung *et al.*[30]	Patients with POAG or ocular hypertension	Randomized double-masked cross over study	60	Placebo in the morning and latanoprost 0.005% in the evening×4 weeks	Unoprostone 0.12% twice daily×4 weeks	4 weeks	Days 2, 14, and 28	Latanoprost was found to be more effective than unoprostone and this difference was a significant one. The mean difference in IOP between the two groups was 3.8 mm.

Contd...

Table 1: Contd...

RCT/Ref	Study group	Study method	No. of subjects	Intervention	Control	Treatment duration	Time points of evaluations	Result
Saito *et al*.[31]	POAG patients	RCT	52	Latanoprost 0.005% once daily×6 weeks, followed by latanoprost 0.005% + unoprostone 0.12% twice daily×6 weeks	Unoprostone 0.12% once daily×6 weeks, followed by latanoprost 0.005% + unoprostone 0.12% twice daily×6 weeks	12 weeks	Weeks 2,4,6,8,10,12	At week 6, IOP reduction in the latanoprost group was 5.5 mm (26.2%), whereas the unoprostone group showed an IOP reduction of 2.7 mm (14.5%). Latanoprost is as effective as a combination of latanoprost+unoprostone
Sponsel *et al*.[32]	OAG patients and glaucoma suspects	RCT	25	Latanoprost 0.005% once daily and placebo once daily in one eye	Unoprostone 0.12% twice daily	4 weeks	Day 28 and week 5	Latanoprost produced a statistically significant reduction in IOP and an increase in pulsatile ocular blood flow compared to unoprostone twice daily. After 4 weeks, the latanoprost group showed an IOP reduction of 14.5 mm (22%) compared to 15.9 mm (13%) in the unoprostone group.
Susanna *et al*.[33]	Patients with POAG or ocular hypertension	RCT	108	Latanoprost once daily+placebo once daily×8 weeks	Unoprostone twice daily×8 weeks	8 weeks	Weeks 2 and 8	Latanoprost was significantly more effective than unoprostone in reducing IOP. At 8 weeks, IOP reduction was 6.7 mm (28%) for latanoprost and 3.3 mm (14%) for unoprostone.

the exclusion and inclusion criteria, 24 articles were included in the study [Figure 1].

An evaluation of the quality of the research was conducted using the JADAD score. This score gives a weightage of the quality of the RCT out of a total of 5. One point each is assigned if the study is an RCT, is double-blinded, and whether there was a description of dropouts/failures. One additional point was assigned if the method of randomization was described and appropriate and one point if the method of double-blinding was described and appropriate. The score ranges from 0 (bad) to 5 (excellent).[11] The average JADAD value of the researches was found to be 2.83.

RESULTS

There were 24 randomized studies involving PG analogs, some comparing 2 agents and some 3 or 4 agents [Table 1]. The total number of patients included in these studies was 2345. RCTs in the review were from 2001 to 2019. There were five RCTs comparing tafluprost to other agents.[12-16] Fourteen RCTs evaluated the action of travoprost,[7,8,12,15,17-26] and 18 RCTs evaluated latanoprost.[12-14,16,17,19-21,23,24,26-33]

There were 15 RCTs comparing bimatoprost to other prostaglandin analogs.[7,8,12,17,18-28] The level of lowering mean IOP in these studies ranged from 23% to 40.5%. Ten studies were retrieved that compared the IOP lowering effect of bimatoprost to latanoprost, some of them comparing it with other PG analogs as well.[12,17,18,20,21,23,24,26-28] Bimatoprost was found to be more effective than latanoprost in most of the studies. The difference in mean IOP lowering at 3 months ranged from 2.3%[27] to as much as 8%.[12] Two studies showed that the difference in the IOP reducing ability of bimatoprost relative to latanoprost increased at 6 months,[12,28] When compared to the values at 3 months and one study found the difference at 3 months to be significant compared to the IOP difference at 6 months.[26] Thirteen studies were found in which the action of bimatoprost could be compared to travoprost.[7,8,12,17-22,24-26] No study found bimatoprost to be inferior to travoprost. Bimatoprost was found to be more effective in IOP reduction than travoprost in all but two studies.[22,25] One research found the difference in mean IOP lowering of bimatoprost to be as much as 10.5% more than travoprost at 3 months.[12] Two studies were noted in which the effect of bimatoprost could be compared to tafluprost.[12,17] El Hajj Moussa noted that the IOP lowering ability of bimatoprost was 6% more than tafluprost at 3 months.[12] There were no RCTs found to compare unoprostone and bimatoprost. The most common ocular adverse effect of

bimatoprost was ocular hyperemia, and most studies found it to be more commoner in bimatoprost than in other PG analogs. Gandolfi *et al*.[27] noticed that ocular hyperemia was more with bimatoprost than latanoprost and this difference in ocular hyperemia was statistically significant.

There were 18 RCTs comparing the effect of latanoprost to other PG analogs. The range of lowering of mean IOP at 3 months ranged from 14%[29] to 31%.[13] Most of the RCTs comparing latanoprost and bimatoprost show that bimatoprost is more effective in IOP lowering than latanoprost. A comparison between latanoprost and travoprost could be done in seven RCTs.[12,17,19-21,23,26] Four of these RCTs found travoprost to be slightly stronger than latanoprost in lowering mean IOP,[17,19,20,26] but the difference was not significant. Parrish *et al*.[21] found latanoprost to be slightly stronger and the other two studies had equivocal findings. Five studies were retrieved in which latanoprost could be compared to tafluprost.[12-14,16,17] Most of these studies show that tafluprost was slightly more potent in IOP lowering than latanoprost. Park *et al*.[16] showed that tafluprost had more IOP lowering efficacy than latanoprost by almost 12%. Konstas *et al*.[14] found that latanoprost was slightly stronger than tafluprost whereas El Hajj Moussa *et al*.[12] found almost similar IOP lowering ability. Latanoprost was found to be stronger than unoprostone in all the five RCTs comparing their actions.[29-33] Latanoprost was found to be more effective in reducing mean IOP than unoprostone, the difference being 5% to 14% in various studies. Latanoprost was found to be the best-tolerated PG analog, and the incidence of conjunctival hyperemia was lower than the other agents.[13,21,26-28]

Thirteen RCTs compared the action of travoprost to one or more other PG analogs.[7,8,12,15,17-24,26] The IOP lowering at 3 months ranged from 19% to 31% in various studies. Bimatoprost was found to be superior to travoprost in most studies, but trials comparing travoprost to latanoprost found it to be slightly superior to latanoprost. RCTs comparing travoprost and tafluprost found almost similar mean IOP lowering ability of both the agents,[12,17] but Shin *et al*.[15] demonstrated that travoprost had more IOP lowering effect than tafluprost, the difference being to the extent of 4.5%. Regarding the adverse effects, the most common adverse effect noted was ocular hyperemia. Although two studies[18,23] found equal ocular tolerability among all agents, but many RCTs found that travoprost caused ocular hyperemia which was more than latanoprost but less compared to bimatoprost.[8,20,21,22,26]

There were six RCTs in which the action of tafluprost could be compared to other PG analogs.[12-17] IOP lowering at 3 months ranged from 24.1%[16] to 33%.[12] Ge *et al*. found that the adverse effects of tafluprost were more compared to latanoprost, but others did not find any significant differences.[13]

There were five RCTs comparing the action of unoprostone to latanoprost, all found latanoprost to be more effective in lowering IOP compared to unoprostone.[29-33]

DISCUSSION

The present review analyzed 24 RCTs involving PG analogs [Table 1]. Bimatoprost was found to be the most effective PG analog as far as mean IOP lowering was concerned. Different studies showed the IOP lowering ranging from 23% to 40.5%, with most of the studies showing a reduction of about 30–35%. The IOP reduction persisted at 3 months and 6 months. On comparing with other systematic reviews of PG analogs, the results were similar,[10,34,35] except that of Li *et al*.[36] who found that travoprost has similar efficacy as bimatoprost.

The present study noted that travoprost, tafluprost, and latanoprost had almost similar IOP lowering efficacy with more studies showing that travoprost was slightly stronger than tafluprost, which in turn was found to be slightly stronger than latanoprost. Latanoprost showed an IOP reduction ranging from 14% to 31%, with an average IOP lowering of 27–30% in most of the studies. The range of IOP lowering of travoprost ranged from 19% to 31%, and tafluprost from 24% to 33%. Tang *et al*.[10] found similar efficacy between travoprost and latanoprost. Li *et al*.[34] found latanoprost to have more effect in IOP lowering than travoprost and tafluprost. Li noted similar efficacy between travoprost and latanoprost.[36] Unoprostone was found to be the least effective of the PG analogs. Its twice-daily dosage is an additional disadvantage.

The absence of systemic adverse effects is an important advantage of this group of medications. However, the most common adverse effect of the PG analogs was found to be ocular hyperemia. An analysis of the RCTs showed that bimatoprost was most commonly associated with ocular hyperemia and latanoprost the least. Travoprost and tafluprost were noted to have more incidence of hyperemia than latanoprost. This was similar to the results of other systematic reviews.[10,34-36] As demonstrated by Stalmans *et al*.,[28] preservative-free unit dose formulation help in IOP control and better patient tolerance.

CONCLUSION

Bimatoprost was found to be the most effective in IOP lowering among the antiglaucoma medications, but it is

found to have a higher incidence of ocular adverse effects compared to other PG analogs. Latanoprost was found to have a good IOP lowering profile and the best ocular tolerability. Travoprost and tafluprost had intermediate tolerability. This review also noted that travoprost, tafluprost, and latanoprost had almost similar IOP lowering efficacy. More RCTs with a larger population are needed to evaluate newer agents like tafluprost in more detail. Preservative-free formulations of the PG analogs would go a long way in reducing IOP as well as in preserving ocular surface health and enhancing patient comfort.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Giuffre G. The effects of prostaglandin F2a in the human eye. Graefes Arch Clin Exp Ophthalmol 1985;222:139—41.
2. Bean GW, Camras CB. Commercially available prostaglandin analogs for the reduction of intraocular pressure: Similarities and differences. Surv Ophthalmol 2008;53(Suppl 1):S69-84.
3. Perry CM, McGavin JK, Culy CR, Ibbotson T. Latanoprost: An update of its use in glaucoma and ocular hypertension. Drugs Aging 2003;20:597-630.
4. Bazzaz S, Myers JS, Katz LJ. Travoprost in the treatment of glaucoma Travoprost in the treatment of glaucoma. Expert Rev Ophthalmol 2007;2:177-83.
5. Pantcheva MB, Seibold LK, Awadallah NS, Kahook MY. Tafluprost: A novel prostaglandin analog for treatment of glaucoma. Adv Ther 2011;28:707-15.
6. Kara C, Şen EM, Elgin KU, Serdar K, Yilmazbaş P. Does the intraocular pressure-lowering effect of prostaglandin analogues continue over the long term?. Int Ophthalmol 2017;37:619-26.
7. Noecker RJ, Earl ML, Mundorf TK, Silverstein SM, Phillips MP. Comparing bimatoprost and travoprost in black Americans. Curr Med Res Opin 2006;22:2175-80.
8. Cantor LB, Hoop J, Morgan L, Wudunn D, Catoira Y, Bimatoprost-Travoprost Study Group. Intraocular pressure-lowering efficacy of bimatoprost 0.03% and travoprost 0.004% in patients with glaucoma or ocular hypertension. Br J Ophthalmol 2006;90:1370-3.
9. Huang HL, Sun XH, Xiao M. Comparison of intraocular pressure reducing effects of three prostaglandin eyedrops in open-angle glaucoma. Zhonghua Yan Ke Za Zhi 2011;47:109-13.
10. Tang W, Zhang F, Liu K, Duan X. Efficacy and safety of prostaglandin analogues in primary open-angle glaucoma or ocular hypertension patients: A meta-analysis. Medicine (Baltimore) 2019;98:e16597.
11. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, *et al*. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 1996;17:1-2.
12. El Hajj Moussa WG, Farhat RG, Nehme JC, Sahyoun MA, Schakal AR, Jalkh AE, *et al*. Comparison of efficacy and ocular surface disease index score between bimatoprost, latanoprost, travoprost, and tafluprost in glaucoma patients. J Ophthalmol 2018;2018:1319628. doi: 10.1155/2018/1319628.
13. Ge J, Li X, Sun X, He X, Zhang H. Randomized parallel group study of 0.0015% tafluprost ophthalmic solution in patients with primary open-angle glaucoma or ocular hypertension (comparison with 0.005% latanoprost ophthalmic solution). Zhonghua Yan Ke Za Zhi 2015;51:95-102.
14. Konstas AG, Quaranta L, Katsanos A, Riva I, Tsai JC, Giannopoulos T, *et al*. Twenty-four hour efficacy with preservative free tafluprost compared with latanoprost in patients with primary open angle glaucoma or ocular hypertension. Br J Ophthalmol 2013;97:1510-5.
15. Shin J, Lee JW, Choi BS, Yun EY, Jung JH, Kim EA, *et al*. The circadian changes of intraocular pressure and ocular perfusion pressure after tafluprost compared with travoprost in normal tension glaucoma. J Ocul Pharmacol Ther 2014;30:803-9.
16. Park SH, Yoo SH, Ha SJ. Comparison of ocular pulse amplitude-lowering effects of tafluprost and latanoprost by dynamic contour tonometry. J Ocul Pharmacol Ther 2015;31:617-22.
17. Kawaguchi I, Higashide T, Ohkubo S, Kawaguchi C, Sugiyama K. Comparison of efficacy of four prostaglandin analogues by bilateral treatment in healthy subjects. Jpn J Ophthalmol 2012;56:346-53.
18. Chander A, Kapoor H, Thomas S. Comparison of the efficacy and safety of bimatoprost (0.03%) and travoprost (0.004%) in patients with primary open angle glaucoma. Nepal J Ophthalmol 2013;5:75-80.
19. Hepsen IF, Ozkaya E. 24-h IOP control with latanoprost, travoprost, and bimatoprost in subjects with exfoliation syndrome and ocular hypertension. Eye (Lond) 2007;21:453-8.
20. Mishra D, Sinha BP, Kumar MS. Comparing the efficacy of latanoprost (0.005%), bimatoprost (0.03%), travoprost (0.004%), and timolol (0.5%) in the treatment of primary open angle glaucoma. Korean J Ophthalmol 2014;28:399-407.
21. Parrish RK, Palmberg P, Sheu WP; XLT Study Group. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: A 12-week, randomized, masked-evaluator multicenter study. Am J Ophthalmol 2003;135:688-703.
22. DuBiner HB, Hubatsch DA. Late-day intraocular pressure-lowering efficacy and tolerability of travoprost 0.004% versus bimatoprost 0.01% in patients with open-angle glaucoma or ocular hypertension: A randomized trial. BMC Ophthalmol 2014;14:151.
23. Crichton AC, Vold S, Williams JM, Hollander DA. Ocular surface tolerability of prostaglandin analogs and prostamides in patients with glaucoma or ocular hypertension. Adv Ther 2013;30:260-70.
24. Blondeau P, Hamid M, Ghalie Z. Prospective randomized clinical trial on the effects of latanoprost, travoprost and bimatoprost on latanoprost non-responders. J Fr Ophtalmol 2019;42:894-9.
25. Frenkel RE, Noecker RJ, Craven ER. Evaluation of circadian control of intraocular pressure after a single drop of bimatoprost 0.03% or travoprost 0.004%. Curr Med Res Opin 2008;24:919-23.
26. Faridi UA, Saleh TA, Ewings P, Venkateswaran M, Cadman DH, Samarasinghe RA, *et al*. Comparative study of three prostaglandin analogues in the treatment of newly diagnosed cases of ocular hypertension, open-angle and normal tension glaucoma. Clin Exp Ophthalmol 2010;38:678-82.
27. Gandolfi S, Simmons ST, Sturm R, Chen K, VanDenburgh AM; Bimatoprost Study Group 3. Three-month comparison of bimatoprost and latanoprost in patients with glaucoma and ocular hypertension. Adv Ther 2001;18:110-21.
28. Stalmans I, Oddone F, Cordeiro MF, Hommer A, Montesano G, Ribeiro L, *et al*. Comparison of preservative-free latanoprost and preservative-free bimatoprost in a multicenter, randomized, investigator-masked cross-over clinical trial, the SPORT trial. Graefes Arch Clin Exp Ophthalmol 2016;254:1151-8.
29. Takemoto D, Higashide T, Saito Y, Ohkubo S, Udagawa S, Takeda H, *et al*. Intraocular pressure and visual field changes in normal-tension glaucoma patients treated using either unoprostone or latanoprost: A prospective comparative study. Clin Ophthalmol 2017;11:1617-24.
30. Aung T, Chew PT, Yip CC, Chan YH, See JL, Khng CG. A randomized double-masked crossover study comparing latanoprost 0.005% with

unoprostone 0.12% in patients with primary open-angle glaucoma and ocular hypertension. Am J Ophthalmol 2001;131:636-42.
31. Saito M, Takano R, Shirato S. Effects of latanoprost and unoprostone when used alone or in combination for open-angle glaucoma. Am J Ophthalmol 2001;132:485-9.
32. Sponsel WE, Paris G, Trigo Y, Pena M. Comparative effects of latanoprost (Xalatan) and unoprostone (Rescula) in patients with open-angle glaucoma and suspected glaucoma. Am J Ophthalmol 2002;134:552-9.
33. Susanna R Jr, Giampani J Jr, Borges AS, Vessani RM, Jordao ML. A double-masked, randomized clinical trial comparing latanoprost with unoprostone in patients with open-angle glaucoma or ocular hypertension. Ophthalmology 2001;108:259-63.
34. Li T, Lindsley K, Rouse B, Hong H, Shi Q, Friedman DS. Comparative effectiveness of first-line medications for primary open-angle glaucoma: A systematic review and network meta-analysis. Ophthalmology 2016;123:129-40.
35. Cheng JW, Wei RL. Meta-analysis of 13 randomized controlled trials comparing bimatoprost with latanoprost in patients with elevated intraocular pressure. Clin Ther 2008;30:622-32.
36. Li N, Chen XM, Zhou Y, Wei ML, Yao X. Travoprost compared with other prostaglandin analogues or timolol in patients with open-angle glaucoma or ocular hypertension: Meta-analysis of randomized controlled trials. Clin Exp Ophthalmol 2006;34:755-64.

"Ousted little elf"—Secondary glaucoma in Weill-Marchesani syndrome

ABSTRACT

Ocular features of Weill-Marchesani syndrome include ectopia lentis, myopia, and pupillary block glaucoma. The purpose of this case report is to describe a case of secondary glaucoma in an 18-year-old female with suspected Weill-Marchesani syndrome.

Keywords: Ectopia lentis, Pupillary block glaucoma, Weill-Marchesani syndrome

INTRODUCTION

Weill-Marchesani syndrome has varied ocular, musculoskeletal, and cardiovascular manifestations.[1] Ocular features include microspherophakia, myopia, ectopia lentis, and glaucoma.

An 18-year-old female with a history of defective vision in both eyes for 10 years associated with photophobia was presented to the glaucoma clinic of our institution. She was using spectacles for compound myopic astigmatism. She had undergone laser peripheral iridotomy in both eyes 3 years ago and was using Timolol eyedrops in both her eyes.

She had a height of 147 cm and no family history of defective vision.

On examination, her best corrected visual acuity was counting fingers at 1 m improving (with -12.00D Sph -3.00Cyl at 7 0degree OD and -17.00D Sph -3.00Cyl at 110 degrees OS) to 6/12. Anterior segment examination revealed in complete anterior dislocation of the crystalline lens in the right eye [Figure 1a and b] with patent peripheral iridotomies and shallow angles in both eyes [Figure 2]. Gonioscopy revealed closed angles in all quadrants in both eyes. Intraocular pressure was 16 mm of Hg in the right eye and 23 mm of Hg in the left eye.

Submitted: 02-Jun-2023 **Accepted:** 03-Jun-2023 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	Quick Response Code
DOI: 10.4103/kjo.kjo_65_23	

She had brachydactyly with joint stiffness and joint deformities [Figure 3]. Rheumatology consultation and cardiology consultation were done. Echocardiogram showed mild aortic regurgitation. She is now on regular follow-up.

Lens removal with trabeculectomy was planned in both eyes (right eye followed by left).

DISCUSSION

Weill-Marchesani syndrome (WMS), described by Weill in 1932 and further defined by Marchesani in 1939, is characterized by lens abnormalities, short stature, brachydactyly, joint stiffness, and cardiovascular abnormalities.[2] WMS can be inherited sporadically, in autosomal dominant or recessive form. Mutations in fibrillin, the structural scaffold protein, play the culprit in WMS. Fibrillin is present in ciliary zonules, blood vessels, dermis, and connective tissue of lungs, and fibrillin-1 mutations lead to disruption in heparan sulfate binding in TB domain (TB5), resulting in varied clinical manifestations.[3] Pathological variations in ADAMTS10, ADAMTS17, LTBP2, and FBN1 genes have been reported.[4,5]

Devi Karthya

Senior Resident, Regional Institute of Ophthalmology, Trivandrum, Kerala, India

Address for correspondence: Dr. Devi Karthya, Department of Ophthalmology, Regional Institute of Ophthalmology, Trivandrum, Kerala, India.
E-mail: devikarthya@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Karthya D. "Ousted little elf"—Secondary glaucoma in Weill-Marchesani syndrome. Kerala J Ophthalmol 2023;35:139-40.

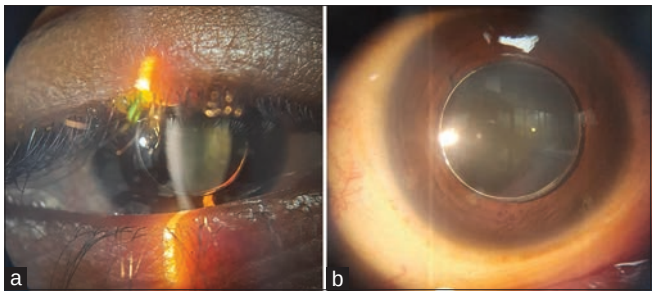


Figure 1: (a Anterior dislocation of lens (RE) b)

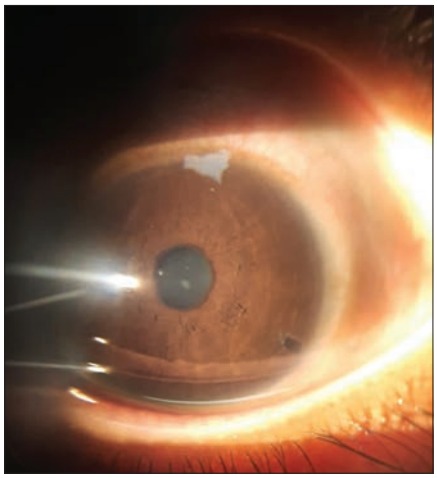


Figure 2: Shallow anterior chamber, post-PI (LE)



Figure 3: Brachydactyly with joint deformity

The ensuing zonular weakness and the highly mobile lens lead to pupillary block with anterior dislocation of the lens. Microspherophakia and lenticular myopia have been recognized in WMS. A thorough physical examination is pivotal to identify other clinical features. Genetic testing using exome sequencing is commonly used in cases of high clinical suspicion.[6]

Early detection and removal of ectopia lentis, peripheral iridectomy to relieve pupillary block, and trabeculectomy in advanced angle close have been advocated.[1,7-9] Systemic symptoms need a multidisciplinary approach including physical therapy for the joint condition, serial monitoring of echocardiogram, and electrocardiogram for cardiology follow-up.[10]

Declaration of patient consent

The authors certify that all appropriate patient consent has been obtained. Patient understands that the names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Damji KF, Moroi SE, Rhee DJ, Freedman SF, Asrani SG, Teng CC. Sheilds textbook of glaucoma.7th ed. New Delhi: Wolters Kluwer (India); 2020.
2. Levitas A, Aspit L, Lowenthal N, Shaki D, Krymko H, Slanovic L, *et al*. A novel mutation in the ADAMTS10 associated with Weil–Marchesani syndrome with a unique presentation of developed membranes causing severe stenosis of the supra pulmonic, supramitral, and subaortic areas in the heart. Int J Mol Sci 2023;24:8864.
3. Ashworth JL, Kielty CM, McLeod D. Fibrillin and the eye. Br J Ophthalmol 2000;84:1312-7.
4. Weill-Marchesani Syndrome. Genetic and Rare Diseases Information Center (GARD). 2017. Available from: https://rarediseases.info.nih.gov/diseases/4936/weill-marchesani-syndrome. [Last accessed on 2021 Mar 01].
5. Miao N, Zhang Y, Liao JY, Zhou L, He JC, Yang RQ, *et al*. Novel homozygous ADAMTS17 missense variant in Weill-Marchesani syndrome. Int J Ophthalmol 2023;16:694-9.
6. Cain SA, McGovern A, Baldwin AK, Baldock C, Kielty CM. Fibrillin-1 mutations causing Weill-Marchesani syndrome and acromicric and geleophysic dysplasias disrupt heparan sulfate interactions. PLoS One 2012;7:e48634.
7. Thattaruthody F, Akella M, Dhingra D, Pandav SS, Kaushik S. Weill-Marchesani syndrome with secondary angle closure glaucoma. J Glaucoma 2019. doi: 10.1097/IJG.0000000000001399. PMID: 31688372.
8. Guo H, Wu X, Cai K, Qiao Z. Weill-Marchesani syndrome with advanced glaucoma and corneal endothelial dysfunction: A case report and literature review. BMC Ophthalmol 2015;15:3.
9. Asaoka R, Kato M, Suami M, Usami Y, Hotta Y, Sato M. Chronic angle closure glaucoma secondary to frail zonular fibres and spherophakia. Acta Ophthalmol Scand 2003;81:533-5.
10. Kojuri J, Razeghinejad MR, Aslani A. Cardiac findings in Weill-Marchesani syndrome. Am J Med Genet A 2007;143A:2062-4.

Original Article

Efficacy of topical immunotherapy in the management of Ocular Surface Squamous Neoplasia (OSSN)– A retrospective analysis

ABSTRACT

Purpose: To evaluate the efficacy of topical immunotherapy with Interferon α 2b [INF- α 2b] drops with a concentration of 3 million international units per millilitre (3 MIU/ml), in the treatment of noninvasive Ocular Surface Squamous Neoplasia (OSSN). **Methods:** A retrospective case record-based study of patients with noninvasive OSSN, who were treated with INF- α 2b drops (3 MIU/ml) during the period from January 2016 to January 2020 at a tertiary care centre in South India. The demographic details, clinical findings, slit lamp photographs, investigations, histopathological records, clinical course, mean duration of clinical and cytological resolution, any evidence of intolerance to treatment, failure to treatment, and recurrences were analysed. **Results:** Fourteen eyes of 12 patients were studied. The majority of patients were male (83%) and aged more than 50 years (83%). 64.28% of cases became disease free clinically and histopathologically in 3 months. 21.4% of cases showed partial resolution. **Conclusion:** Topical immunotherapy is an effective mode of treatment for noninvasive OSSN. The 3 MIU/mL dose of topical IFN-a2b drops helped in faster resolution. No recurrences were reported. No severe surface toxicity or intolerance was observed.

Keywords: Immunotherapy, interferon alpha 2b, OSSN

INTRODUCTION

Ocular Surface Squamous Neoplasia (OSSN) includes the entire spectrum of dysplastic, preinvasive, and malignant squamous lesions of conjunctiva and cornea and typically presents as pearly gray growth with feeder vessels.[1] UV-B light,[2] human papilloma virus 16, HIV seropositivity,[3-5] and stem cell defects[6] are some of the etiological factors attributed for OSSN. Morphologically OSSN can be conjunctival or corneal types.[7] Conjunctival lesions can be placoid, nodular, and diffuse. Placoid is further subdivided into leukoplakic, gelatinous, and papilliform (exophytic, strawberry like lesions). Corneal lesions usually have a mottled ground glass sheet appearance. Advanced cases may infiltrate the cornea and sclera and lead to intraocular extension. The tumour may rarely extend into the orbit causing proptosis. The tumour may metastasize to the regional lymph nodes and very rarely distant metastasis may occur.[7]

Confirmatory investigations for OSSN include excision biopsy and impression cytology.[8-10] Adjunct investigations to detect any intraocular or distant metastasis include B scan, anterior segment OCT, regional lymph node examination, CT and MRI of the orbit, and brain and oncology evaluation.[7] Serological tests for HIV and HBsAg are mandatory as OSSN has a higher

Sinumol S. Thulaseedharan[1], Ajithkumar V Raghavan[2], Ashwati Sankar[3], Sujatha N[1], Sudha Vaikkakara[4], Devu Krishna T[1]

[1]Department of Ophthalmology, Government Medical College, Thrissur, Kerala, [2]Department of Radiotherapy, Government Medical College, Thiruvananthapuram, Kerala, [3]Department of Ophthalmology, MES Medical College, Perinthalmanna, Kerala, [4]Department of Ophthalmology, Government Medical College, Idukki, Kerala, India

Address for correspondence: Dr. Devu Krishna T, Adwaitham, Green Lane, M G Kavu P O, Thrissur, Kerala, India. E-mail: devukrishnat@gmail.com

Submitted: 02-Oct-2022 **Accepted:** 29-Nov-2022 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	Quick Response Code
DOI: 10.4103/kjo.kjo_109_22	

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Thulaseedharan SS, Raghavan AV, Sankar A, Sujatha N, Vaikkakara S, Krishna TD. Efficacy of topical immunotherapy in the management of Ocular Surface Squamous Neoplasia (OSSN)– A retrospective analysis. Kerala J Ophthalmol 2023;35:141-8.

incidence in HIV patients.[3-5] The various treatment options for OSSN include surgical excision with wide margin (4 mm) by 'No-touch' technique, absolute alcohol epitheliectomy of the involved cornea, and cryotherapy in a double freeze–thaw cycle to the limbus and conjunctival margins.[11] Complications like limbal stem cell loss and recurrence of tumour due to incomplete excision are possible. Chemotherapy with topical Mitomycin C (MMC) and 5-Fluorouracil are effective, but complications like corneal epitheliopathy and scleral ulceration are common.[12] Previous studies have shown the effectiveness and safety of topical immunotherapy in the management of OSSN.[13-15] Immunotherapy with Interferon α 2b (INF- α 2b) has been used as an off-label therapy in OSSN.[16] INF α2b is a type 1 interferon (INF) consisting of 165 amino acid residues with arginine in position 23. This is produced by recombinant DNA technology.[17,18] It exhibits antineoplastic and antiviral effects.[17,18] It can be used as topical medication, either as drops or perilesional injection or in a combined manner without much local toxicity. We evaluated the efficacy of topical immunotherapy with Interferon α 2b (INF- α 2b) in the treatment of noninvasive OSSN at a tertiary care centre in South India.

METHODS

We did a retrospective case record-based study of patients with OSSN who were treated with INF α2b during the period January 2016 to January 2020 in the departments of Ophthalmology and Oncology in our institution. The study was conducted after approval by the institutional ethics committee. The study materials included case records of all patients with noninvasive OSSN [Tis, T1, T2 by American Joint Committee on Cancer (AJCC) classification [Table 1] who were diagnosed clinically and confirmed with impression cytology and underwent topical immunotherapy with Interferon α 2b (INF- α 2b) drops 3 MIU/mL and followed-up for at least 12 months post-treatment. We excluded cases of invasive OSSN, extensive OSSN with primary tumour above T 3 by AJCC classification [Table 1], lymph node involvement, or distant metastasis. All cases treated with surgery and chemotherapy as the first-line treatment were also excluded. The patients who were recorded as discontinued or noncompliant to treatment or lost to follow-up or with <12 months follow-ups were also excluded from the study.

Protocol for management of OSSN we follow in our institution

Our institution follows the American Joint Committee Classification, 7th edition management protocol for OSSN.[7] We routinely do impression cytology for histopathological confirmation of OSSN before starting the treatment, as it is noninvasive. Biopsy is done if the findings of impression cytology are suspicious/negative/inconclusive. Routine investigations and serological tests for HIV are done for all patients. A complete ophthalmological examination along with slit lamp photography, anterior segment OCT, and B scan are done for all patients. Regional lymph node examination and medical examination to rule out local, regional, or systemic metastasis were performed in all cases with necessary investigations and imaging techniques by the Oncology department. The primary tumour will be classified based on the American Joint Committee Classification, 7th edition. [Table 1].

Table 1: American Joint Committee on Cancer (AJCC)-tumour, node, and metastasis (TNM) classification*

Clinical Category	Definition
Primary Tumour - Tx	Tumour cannot be assessed
T0	Tumour absent
Tis	Carcinoma in situ/conjunctival intraepithelial neoplasia
T 1	Tumour present with largest basal diameter≤5 mm
T 2	Tumour present with largest basal diameter≥5 mm, no invasion
T 3	Tumour invades adjacent structures †excluding orbit
T 4	Tumour invades the orbit with or without further extension
T 4a	Tumour invades orbital soft tissue without bone invasion
T 4b	Tumour invades bone
T 4c	Tumour invades adjacent paranasal sinus
T 4d	Tumour invades brain
Regional lymph nodes Nx	Regional Lymph Nodes cannot be assessed
N0	Regional Lymph Node metastasis absent
N1	Regional Lymph Nodes metastasis present
Distant Metastasis	
M0	Distant Metastasis absent
M1	Distant Metastasis present

* Credit note: Edge SB, Byrd DR, Comptom CC, editors. 7th ed.. New York, NY: Springer; 2010. AJCC Cancer Staging Manual. † Adjacent structures include cornea, conjunctiva, intraocular compartments, caruncle, canaliculi, semilunar folds, and lacrimal punctum and eyelids.

We routinely discuss the various treatment options available and their benefits and drawbacks with the patients and obtain a written informed consent before starting treatment. For noninvasive OSSN, who opt for immunotherapy, Interferon α 2b (INF- α 2b) solution (3 million IU/ml) is administered as topical drops until complete clinical and cytological resolution and a month thereafter. The drug is reconstituted by mixing injection preparation of Interferon α 2b (3 MIU/0.5 ml) with 0.5 mL of refrigerated sterile distilled water to get 1 mL in a concentration of 3 MIU/mL. Two vials are reconstituted at a time to get 2 mL of drops. We provide this to patients in ice packs for transport and they are advised to keep this solution at 4°C-8°C in refrigerator as soon as they reach home or at least within 5 hours. This solution is to be used as topical

therapy to the eye, one drop 4 times daily at an interval of 6 hours. Patients are advised punctal occlusion for 5 minutes after instillation of drops. The reconstituted drops are replaced weekly.

These patients are to be routinely reviewed every week for the duration of treatment and at monthly intervals thereafter for 1 year. The best-corrected visual acuity, maximal tumour basal diameter, tumour surface area, and interferon alfa-2b–related toxicity are recorded at each of the follow-up visits. Clinical photographs and impression cytology are taken at presentation and at monthly intervals for up to 6 months or up to complete resolution whichever is longer, then at 9 months and 1 year. Oncology check-up is a must for all patients at diagnosis and then at every 3 months up to 1 year and then at yearly intervals.

Patients will be advised surgery (wide excision and biopsy) or a change to topical chemotherapy with MMC, if they do not show significant tumour reduction even after 8 weeks of immunotherapy, after discussing with Oncologist. All the data are kept as hard copy and soft copy in dedicated folders in the records library, after obtaining informed consent from the patients, for possible use of data for research purposes also.

Study Procedure

For this study, the demographic details, presenting complaints, duration of symptoms, history of HIV infection, systemic malignancies, and history of similar illness in the past were retrieved from the case records. Details of the slit lamp assessment of OSSN at presentation and on follow-ups were retrieved. These included the tumour laterality, tumour location and extent (conjunctiva, cornea, conjunctival-limbal-corneal surface), maximum basal tumour diameter (mm), number of limbal clock hours involved by the tumour, and tumour pattern [leukoplakic, gelatinous, nodular, papillary, placoid, and pigmented] [Figure 1], and the presence and number of the feeder vessels and ground glass appearance in the cornea. Slit lamp photographs of each patient [Figures 1-3], details of anterior segment OCT, dilated fundus examination, and B scan were retrieved from the case records. The details of histopathological confirmation [impression cytology photographs and reports at presentation and on follow-ups [Figure 4a-c] were also obtained. Reports of any side effects or intolerance to INF α2b and any other treatments given for further tumour control were noted. Evidence of local or distant metastasis as recorded in oncology reviews, if any, were also noted.

The clinical course, the mean duration of clinical resolution, the mean duration of cytological resolution, any intolerance

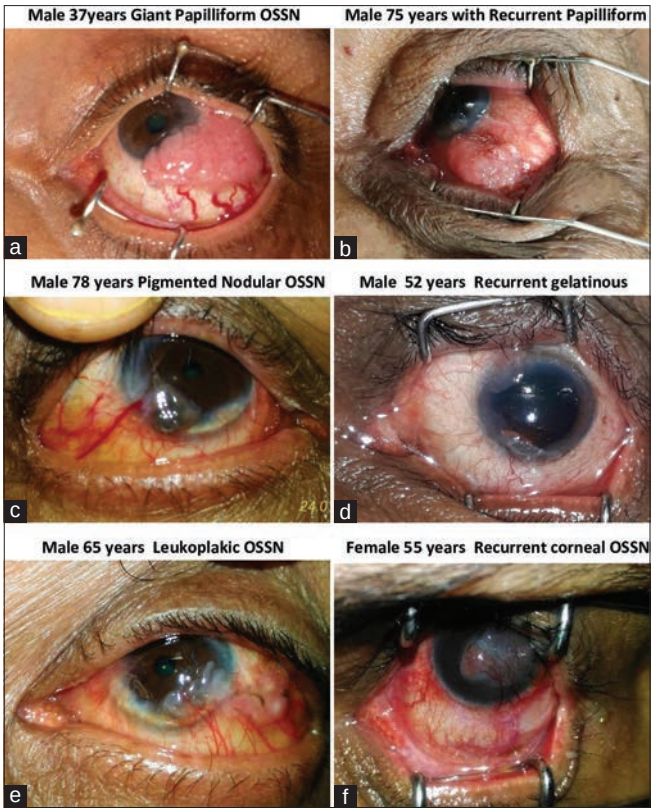


Figure 1: (a) Giant papilliform OSSN in a 37 year old male patient, (b) Recurrent papilliform OSSN in a 75 year old male patient, (c) Pigmented nodular OSSN in 78 year old male, (d) Recurrent gelatinous OSSN in a 52 year old male patient, (e) Leukoplakic OSSN in a 65 year old male patient, (f) Recurrent corneal OSSN in a 55 year old female patient

to Interferon α 2b, failure to treatment, and recurrences were analysed from the data [Table 2].

Complete success is defined as 100% tumour reduction clinically and normal squamous cells without any dysplasia by impression cytology, with topical interferon alfa-2b treatment, within a period of 3 months [Figure 2a, 2c, 2d]. Partial success is defined as tumour regression of less than 100% (immunoreduction) with dysplastic cells in impression cytology at 3 months and need for other modalities of treatment for complete resolution [Figures 2b and 3]. Recurrence is defined as the reappearance of a tumour at the same location after complete resolution following treatment. New tumour is defined as the appearance of a tumour at a location distant from the original lesion. Failure to treatment is defined as a nonresponse to INF- α 2b that necessitated change in treatment modality or progression of the disease or local/systemic spread of tumour.

RESULTS

Twenty two eyes of 20 patients of OSSN were diagnosed clinically and confirmed by either impression cytology or by

Table 2: Data of patients included in the study

Age	Sex	Primary/ Recurrent	Morphology	AJCC stage	mean duration of clinical resolution	mean duration of cytology resolution	Any other treatment required	Outcome
82	M	primary	Unilateral Papilliform	$T_2 N_0 M_0$	6 weeks	8 weeks	NIL	Complete success
55	F	Recurrent	Unilateral Corneal	$T_2 N_0 M_0$	12 weeks	9 months	MMC -4 cycles	Partial success
78	M	primary	Unilateral Nodular	$T_1 N_0 M_0$	4 weeks	8 weeks	NIL	Complete success
75	M	primary	Unilateral Leukoplakic	$T_2 N_0 M_0$	6 weeks	8 weeks	NIL	Complete success
37	M	primary	Unilateral Giant Papilliform	$T_2 N_0 M_0$	6 weeks	8 weeks	NIL	Complete success
65	M	primary	Bilateral Leukoplakic	$T_2 N_0 M_0$	8 weeks	12 weeks	NIL	Complete success
75	M	Recurrent	Unilateral Giant Papilliform	$T_2 N_0 M_0$	Less than 25% change	nil	Surgery	Failure
50	M	primary	Unilateral Gelatinous	$T_1 N_0 M_0$	4 weeks	8 weeks	NIL	Complete success
52	M	Recurrent	Unilateral Gelatinous	$T_2 N_0 M_0$	6 weeks	8 weeks	NIL	Complete success
12	M	primary	Bilateral Nodular	$T_2 N_0 M_0$	75% reduction at 12 weeks.	8 months	MMC- 3 cycles	Partial success
78	M	primary	Unilateral Papilliform	$T_2 N_0 M_0$	6 weeks	8 weeks	NIL	Complete success
65	F	primary	Unilateral Nodular	$T_1 N_0 M_0$	No gross change	nil	Surgery	Failure

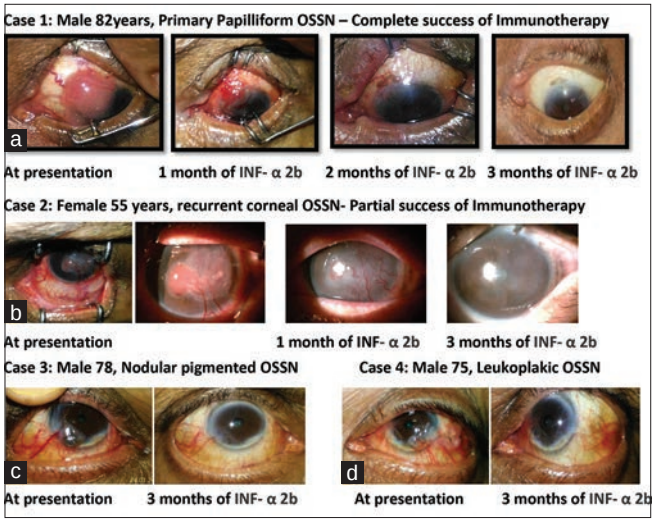


Figure 2: (a) Case 1 - Primary papilliform OSSN in an 82 year old male patient was completely resolved with topical immunotherapy over 3 months, (b) Case 2 - Recurrent Corneal OSSN in a 55 year old female patient showed partial resolution with topical immunotherapy, (c) Case 3 - Primary pigmented nodular OSSN in a 78 year old male patient showed complete resolution with topical immunotherapy over 3 months, (d) Case 4- 78 year old male with Leukoplakic OSSN showed complete resolution over 3 months with topical immunotherapy

biopsy and underwent treatment in our institute during the period from January 2016 to January 2020. Fourteen eyes of 12 patients who met the inclusion criteria were included in this study [Table 2]. The majority of patients were male (83%) and aged more than 50 years (83%).



Figure 3: Case of Xeroderma Pigmentosa with bilateral nodular OSSN (Original)

Nine patients (75%) were primary cases without any history of similar illness in the past. Three patients were considered as recurrent OSSN from their previous clinical records. The 55-year-old female patient with corneal OSSN [Figures 1f and 2b] had previous records of three surgeries (excision pterygium with Amniotic Membrane Transplantation, excision pterygium with limbal stem cell transplantation, and phototherapeutic keratectomy) in the same eye over the previous 2 years in another hospital. The 75-year-old male with a giant papilliform OSSN had records of excision of the previous tumour 1 year back. The

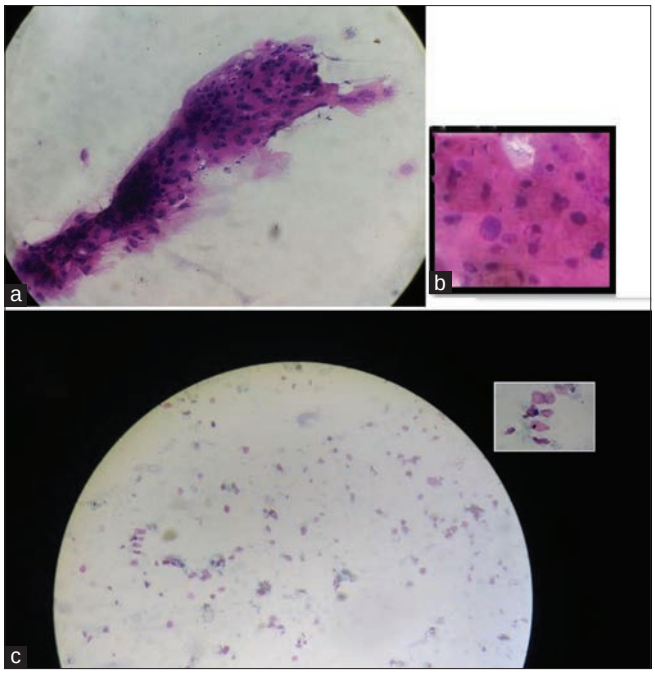


Figure 4: Impression cytology for diagnosis and follow-up of OSSN (Original). (a) Dysplasia in OSSN before treatment. (b) Magnified view–dysplastic cells with nuclear hyperchromasia, prominent nucleoli, pleomorphism, and increased mitotic figures with hyperkeratosis. (c) Normal squamous cells after successful immunotherapy

52-year-old male with gelatinous type OSSN had a history of similar lesion in the same site and resolution with topical chemotherapy 6 months back, which he stopped because of intolerance.

Two patients had bilateral disease. A 65-year-old man, a construction site worker had bilateral leukoplakic OSSN, and a 12-year-old boy with Xeroderma pigmentosa [Figure 3] had bilateral nodular OSSN.

None of the patients were HIV-positive.

Four patients had papilliform type [Figure 1a] of which one was recurrent [Figure 1b]. Three patients had nodular OSSN [Figure 1c]. Two patients were having gelatinous type [Figure 1d]. Two patients presented with Leukoplakic type [Figure 1e] and one patient with corneal OSSN [Figures 1f and 2b].

Nine eyes of 8 patients showed complete success with clinical and histopathological disappearance of OSSN. Slit lamp photos of all these eyes showed dramatic reduction of lesion in 4 weeks and complete clinical resolution in 8 weeks [Figure 2]. Impression cytology reports at 8 weeks were negative for all cases except for one patient with bilateral leucoplakia which later became negative at 12 weeks. Interferon α 2b was stopped at 12 weeks for the first 7 eyes but was continued for 1 more month for the bilateral case. There were no reports of any recurrence or development of new tumour or metastasis during the follow-up period of 1 year. These 9 cases were disease free clinically and cytologically without any additional treatment and categorized as complete success.

The recurrent corneal OSSN clinically resolved well by 3 months, except for the corresponding nebular opacities as evident from the photograph [Figure 2b]. The impression cytology showed dysplastic cells up to 6 months. Her records revealed stoppage of IFN α 2b and further treatment with topical MMC 0.02% four times a day with one week on and one week off in alternating cycles for further 8 weeks. She became cytologically negative at 9 months and remained negative throughout further follow-ups. She was recorded as a partial success.

The only child in the group, a known case of Xeroderma pigmentosa with bilateral nodular OSSN, showed only partial success with more than 75% immunoreduction clinically at 3 months [Figure 3]. There was no further resolution in spite of 6 months of topical Interferon α 2b. He was also treated with topical MMC 0.02% four times a day with one week on and one week off in alternating cycles for further 6 weeks. Records showed that he had complete resolution of the nodular lesion but developed whitening of underlying sclera at the end of 3 cycles. Topical MMC was stopped at this point. He became cytologically negative at 8 months and remained negative throughout further follow-ups.

Two eyes of 2 patients did not show any significant reduction in tumour size even after 8 weeks of interferon therapy. One was a recurrent giant papilliform tumour in a 75-year-old male with a history of previous excision and the other was a 65-year-old female with a nodular type OSSN. Both these patients underwent wide excision biopsy by 'No Touch Technique'. They were categorized as failure of immunotherapy.

Complete tumour resolution clinically and histopathologically [Figure 4c] was achieved in 9 eyes (64.28%) following topical interferon alfa-2b (3 MIU/mL) treatment during a median period of 3 months (range, 2-4 months). Partial success with clinical resolution of more than 75% tumour size obtained in 3 eyes (21.4%) in a 3-month period. Two cases (14.2%) showed a failed response to topical interferon therapy. We did not find any data suggestive of progression of disease, recurrence, development of new tumour, or metastasis during the study period.

Flu-like symptoms for the first few days (9 [75%]), conjunctival hyperemia (4 [28.5%]), and irritation (1 [7%]) were recorded as adverse effects of topical interferon alfa-2b. The adverse effects were mild and resolved within 1 month of stoppage of topical therapy. None of the cases reported allergic reaction or intolerance to interferon and none of the records showed discontinuation of therapy due to side effects.

DISCUSSION

OSSN is the most common ocular surface neoplasm being reported from all over world today. Its clinicopathological behaviour may range from mild dysplasia to invasive malignancy. The dysplastic cells in OSSN are thought to arise from limbal stem cells following various triggering factors including UV radiation. It has been theorized that the human papilloma virus plays a role in development of OSSN.

Most of the patients were male and aged more than 50 years in our series of cases. In many early studies, it was found that elderly males who have lived in geographic areas exposed to high levels of UV-B radiation are more prone to this disease.[1,2]

It is now known that an increased incidence of OSSN has been found in young people with HIV infection and Xeroderma pigmentosa. A study conducted in Africa had shown a high HIV infection rate of 79% in patients with OSSN compared to 14% in the general population.[5] In the United States, a study done at Bascom Palmer Eye Institue found that OSSN may be a possible marker for undiagnosed HIV.[19] The study found that half of patients diagnosed with OSSN aged less than 50 years were seropositive for the virus.[19] Surprisingly, none of our patients were seropositive for HIV but we had a child with Xeroderma pigmentosa who developed bilateral nodular type of OSSN.

The traditional treatment for OSSN is surgical excision with wide margins of about 4 mm and adjuvant cryotherapy.[11,20] However, this can lead to limbal stem cell deficiency, ocular surface irregularity, and scarring, especially when the lesion is a large one. So noninvasive treatments are preferable wherever it is possible.

Primary treatment with topical chemotherapy using MMC and 5-fluorouracil is an effective alternative but has the disadvantage of surface toxicity and increased possibility of scleral necrosis.[12] Topical chemotherapy must be given only under close supervision.

Interferon is a low-molecular weight glycoprotein, with antiviral and antineoplastic activities produced naturally by leukocytes and many other host cells. Interferon alfa-2b is a recombinant form of interferon alfa that is approved by the United States Food and Drug Administration for treatment of chronic hepatitis B and C, malignant melanoma, hairy cell leukemia, multiple myeloma, follicular lymphoma, condyloma acuminata, and AIDS-related Kaposi sarcoma.[21,22]

The use of interferon alfa-2b for OSSN is off-label but supported by scientific evidence.[13-16,22,23] IFN-a2b can be administered as topical drops or as perilesional injections. A typical regimen consists of topical IFN-a2b drops with a concentration of 1 million IU/mL or 3 million IU/mL, applied four times daily or subconjunctival injections of 3 million IU/0.5 mL, administered weekly.

Shah SU *et al.* in their study of 23 cases had reported complete tumour resolution in 19 cases (83%) following topical interferon alfa-2b (1 MIU/ml) treatment 4 times daily for a median period of 6 months (mean, 7 months; range, 1-12 months) and maintained for up to 24 months of follow-up.[15]

The long duration of treatment can negatively affect the compliance of patients and enthusiasm of the treating doctors. Most of the patients get depressed over time which in turn can affect the immune response. A faster resolution is preferable.

Subconjunctival injection combined with topical IFN-a2b for noninvasive OSSN has a faster time to resolution, about six weeks.[24] In one study, the overall response rate was 96.4% and the recurrence rate was 3.7% after 1 year.[25]

The subconjunctival injections of drugs obviate the conjunctival epithelial barrier of drug penetration, which is rate-limiting for permeation of water-soluble drugs and thus the transscleral route bypasses cornea–conjunctiva barrier.[26] This is preferable for drugs that are needed to act intraocularly. In the case of OSSN, the effect will be maximum when the interferon is available over the ocular surface. The slow escape of drug through the injection route and the availability of high concentration in the conjunctival sac might have given the desired effect in the above study.[24]

The drugs administered by periocular injections can also reach systemic circulation through the blood vessels and choroid.[26] This can cause undesirable systemic side effects. Repeated injections into the eye have a detrimental effect in the compliance of patients as most of them are aged and are very intolerant to the pain of subconjunctival injections.

We chose to use 3 MIU/ML topical recombinant drops 4 times daily to address this issue. The medication was kept strictly in cold chain and used within 1 week to maintain the therapeutic efficacy. Freshly reconstituted drops were given every week to continue the therapy. In this study series, we could find out a dramatic response of tumour melting in 4 weeks of topical therapy with IFN-a2b drops (3 MIU/mL) in 85.6% of cases, as evidenced by the clinical photographs and examination reports. Although 2 cases failed to show a significant effect, all other cases showed a rapid response. 64.28% of cases became 100% disease free morphologically and histopathologically in 3 months. 21.4% of cases showed partial success with good immunoreduction of more than 75% of surface area in 3 months period.

Galor A *et al.*[27] compared the effectiveness and side-effect profile of two doses of interferon alpha2b (IFNalpha2b) eye drops (1 million international units [IU]/mL versus 3 million IU/mL) in the treatment of OSSN. They found that there were no statistically significant differences between the 1 million IU/mL group and the 3 million IU/mL group for the treatment of Conjunctival Intraepithelial Neoplasia. But, in patients with Conjunctival Intraepithelial Neoplasia, topical therapy eliminated disease in 81% of eyes in the 1 million IU/mL group versus 92%, in the 3 million IU/mL group, $P = 0.41$. The median time to OSSN resolution was 2.8 months in the 1 million IU/mL group and 1.9 months in the 3 million IU/mL group. This result is similar to our own experience.

There was no incidence of recurrence of tumor or development of new tumor or evidence of metastasis in our series of cases during the follow-up period. Kim H.J. *et al.* also reported that there were no tumor recurrences during a median follow-up of 11 months, but 2 new tumors appeared at a remote site from the original tumor, requiring operative intervention.[28]

As per our treatment protocol, immunotherapy was continued in same dose for 1 more month postresolution in the successful cases. This might be the reason for nil recurrence and absence of development of new tumour in the study period. The topical drops effectively treated the entire ocular surface and all subclinical lesions and may be another reason for reduced recurrence rate. There were no reports of stoppage of drug because of severe local reaction or toxicity to interferon alpha 2b (3 MIU/mL doze) in our series of patients.

Immunotherapy may be a better option of treatment for noninvasive OSSN as it treats the entire ocular surface and all subclinical lesions without much surface toxicity and minimizes the possibility of recurrence. The 3 MIU/mL dose of topical IFN-a2b drops must have helped in faster resolution of tumour. In 85.6% of cases, a dramatic response of tumour melting was evident at 4 weeks. 64.28% of cases became 100% disease free morphologically and histopathologically in 3 months. None of the cases reported serious side effects or recurrence.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Lee GA, Hirst LW. Ocular surface squamous neoplasia. Surv Ophthalmol 1995;39:429–50.
2. Yam JC, Kwok AK. Ultraviolet light and ocular diseases. Int Ophthalmol 2014;34:383-400.
3. Mahomed A, Chetty R Human immunodeficiency virus infection, Bci-2, p53 protein, and Ki-67 analysis in OSSN. Arch Ophthalmol 2002;120:554-8.
4. Thomas JO. Acquired immunodeficiency syndrome-associated cancers in Sub-Saharan Africa. Semin Oncol 2001;28:198-206.
5. Spitzer MS, Batumba NH, Chirambo T, Bartz-Schmidt KU, Kayange P, Kalua K, *et al.* Ocular surface squamous neoplasia as the first apparent manifestation of HIV infection in Malawi. Clin Exp Ophthalmol 2008;36:422-5.
6. Mishra DK, Veena U, Kaliki S, Kethiri AR, Sangwan VS, Ali MH, *et al.* Differential expression of stem cell markers in ocular surface squamous neoplasia. PLoS One 2016;11:e0161800.
7. Honavar SG, Manjandavida FP. Tumors of the ocular surface: A review. Indian J Ophthalmol 2015;63:187-203.
8. Nolan GR, Hirst LW, Wright RG, Bancroft BJ. Application of impression cytology to the diagnosis of conjunctival neoplasms. Diagn Cytopathol 1994;11:246–249.
9. Tole DM, McKelvie PA, Daniell M. Reliability of impression cytology for the diagnosis of ocular surface squamous neoplasia employing the biopore membrane. Br J Ophthalmol 2001;85:154–8.
10. Tananuvat T, Lertprasertsuk N, Mahanupap P, Noppanakeepong P. Role of impression cytology in diagnosis of ocular surface neoplasia. Cornea 2008;27:269–74.
11. Shields JA, Shields CL, DePotter P. Surgical management of conjunctival tumours. Arch Ophthalmol 1997;115:808-15.
12. Kim JW, Abramson DH. Topical treatment options for conjunctival neoplasms. Clin Ophthalmol 2008;2:503-15.
13. Kusumesh R, Ambastha A, Sinha B, Kumar R. Topical interferon

alpha-2b as a single therapy for primary ocular surface squamous neoplasia. Asia Pac J Ophthalmol (Phila) 2015;4:279–82.
14. Vann RR, Karp CL. Perilesional and topical interferon alfa2b for conjunctival and corneal neoplasia. Ophthalmology 1999;106:91-7.
15. Shah SU, Kaliki S, Kim HJ, Lally SE, Shields JA, Shields CL. Topical interferon alfa-2b for management of ocular surface squamous neoplasia in 23 cases: Outcomes based on American Joint Committee on Cancer classification. Arch Ophthalmol 2012;130:159-64.
16. Maskin SL. Regression of limbal epithelial dysplasia with topical interferon. Arch Ophthalmol 1994;112:1145–6.
17. Sepulveda R, Pe'er J, Midena E, Seregard S, Dua HS, Singh AD. Topical chemotherapy for ocular surface squamous neoplasia: Current status. Br J Ophthalmol 2010;94:532–5.
18. Poothullil AM, Colby KA. Topical medical therapies for ocular surface tumors. Semin Ophthalmol 2006;21:161–9.
19. Karp CL, Scott IU, Chang TS, Pflugfelder SC. Conjunctival intraepithelial neoplasia: A possible marker for human immunodeficiency virus infection? Arch Ophthalmol 1996;114:257–261.
20. Giaconi JA, Karp CL. Current treatment options for conjunctival and corneal intraepithelial neoplasia. Ocul Surf 2003;1:66-73.
21. Intron A. Product information: Intron® A interferon alfa-2b, recombinant for injection. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/1997/ifnasch110697-lab.pdf. [Last accessed on 2011 Jan 24].
22. Gangemi JD, Pirisi L, Angell M, Kreider JW. HPV replication in experimental models: Effects of interferon. Antiviral Res 1994;24:175-90.
23. Majewski S, Szmurlo A, Marczak M, Jablonska S, Bollag W. Synergistic effect of retinoids and interferon alpha on tumor-induced angiogenesis: Anti-angiogenic effect on HPV-harboring tumor-cell lines. Int J Cancer 1994;57:81-5.
24. Karp CL, Galor A, Chhabra S, Barnes SD, Alfonso EC. Subconjunctival/perilesional recombinant interferon α2b for ocular surface squamous neoplasia: A 10-year review. Ophthalmology 2010;117:2241-6.
25. Schechter BA, Koreishi AF, Karp CL, Feuer W. Long-term follow-up of conjunctival and corneal intraepithelial neoplasia treated with topical interferon alfa-2b. Ophthalmology 2008;115:1291-6, 1296.e1.
26. Ghate D, Edelhauser HF. Ocular drug delivery. Expert Opin Drug Deliv 2006;3:275–87.
27. Galor A, Karp CL, Chhabra S, Barnes S, Alfonso EC. Topical interferon alpha 2b eye-drops for treatment of ocular surface squamous neoplasia: A dose comparison study. Br J Ophthalmol 2010;94:551-4.
28. Kim HJ, Shields CL, Shah SU, Kaliki S, Lally SE. Giant ocular surface squamous neoplasia managed with interferon alpha-2b as immunotherapy or immunoreduction. Ophthalmology 2012;119:938-44.

Original Article

An observational study on the clinical picture of vernal keratoconjunctivitis at a tertiary care center in Western India

ABSTRACT

Aim: To study the clinical profile and presence of perilimbal pigmentation in cases of vernal keratoconjunctivitis (VKC). **Methods:** This was an observational, cross-sectional study conducted at a tertiary eye care center in western-Maharashtra from March 2019 to February 2020. One hundred fifty-two cases of VKC were identified by history, characteristic symptomatology, and slit-lamp examination. The Statistical Package for the Social Sciences (SPSS) version 20.0 for Windows was used. The relationship of extent of pigmentation with severity and duration of the disease was analyzed using Chi-squared test. A *P* value of less than 0.05 was considered significant. **Results:** Out of 152 cases, 79.61% were males. The mean age at presentation was 11.4 ± 5.62 years. A majority (38.82%) reported in the months of May–June. Most of them had mixed form followed closely by palpebral form. The most common symptom was itching. However, complications like focal-limbal stem-cell deficiency and shield-ulcer were seen in a few cases. Notably, the characteristic perilimbal-bulbar pigmentation was noted in 81 cases (53.29%; 95% CI 45.03%–61.42%; $P < 0.0001$), of which 15 had pigmentation in all the four quadrants ($P = 0.0033$). The extent of pigmentation corelated significantly with the severity of the disease ($P < 0.0001$). However, it did not correlate with the duration of the disease ($P = 0.0794$). **Conclusion:** Studies on VKC in India provide limited epidemiological data, and there has been no significant series that has explained its clinical pattern in the western part of the country. The presence of perilimbal pigmentation may be a diagnostic sign in mild VKC when signs and symptoms are subtle. This knowledge will help in early diagnosis and management and thus, help prevent sight-threatening complications of VKC.

Keywords: Perilimbal pigmentation, upper tarsal papillae, vernal keratoconjunctivitis, Western India

INTRODUCTION

Vernal keratoconjunctivitis (VKC) is an immunologically mediated and hypersensitive reaction to environmental antigens and is characterized by bilateral, severe, chronic inflammation of the ocular surface.[1] It is more prevalent in the male population.[2] It is usually seasonal with higher incidence in hot weather and occasional flare-ups during winters which could lead to chronic and perennial disease.[3] Various forms of VKC have variable global distribution with widely varying incidence, the palpebral form being more prevalent in Europe and America and mixed and limbal forms being more common in Asia and Africa, respectively.[4]

The hallmark characteristic of VKC is the presence of cobblestone-like papillae mainly involving the upper tarsal conjunctiva.[5] Gelatinous-limbal thickening, Horner–Trantas

Mohini Agrawal, Srujana Dubbaka[1], Sumedha Vats[2]

Department of Ophthalmology, Command Hospital, Pune, Maharashtra, [1]Department of Ophthalmology, Armed Forces Medical College, Pune, Maharashtra, [2]Department of Ophthalmology, Armed Forces Clinic, New Delhi, India

Institution where the work was carried out:
Department of Ophthalmology, Armed Forces Medical College, Pune, Maharashtra, India

Address for correspondence: Dr. Mohini Agrawal, Department of Ophthalmology, Command Hospital, Pune, Maharashtra, India.
E-mail: mohiniafmc.15@gmail.com

Submitted: 30-Jan-2022
Accepted: 05-Oct-2022 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	**Quick Response Code**
DOI: 10.4103/kjo.kjo_22_22	

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Agrawal M, Dubbaka S, Vats S. An observational study on the clinical picture of vernal keratoconjunctivitis at a tertiary care center in Western India. Kerala J Ophthalmol 2023;35:149-54.

dots, and corneal involvement are seen in severe cases. A thick, mucoid, ropy discharge is invariably present in the inferior fornix.[6] Among the established features of VKC, a new sign has been described clinically as fine, golden-brown pigmentation located in the perilimbal bulbar conjunctiva[7] and named as perilimbal pigmentation (PLP). It is caused due to increased melanocytic activity in response to inflammation of the surrounding connective tissue.[8]

Andrea Leonardi once wrote, "When you see a child suffering from a severe form of VKC, you instantly feel the dearth in knowledge of pathogenesis that prevents you from adequately treating the clinical signs and symptoms that will most likely ruin his childhood."[9] VKC is a major cause of hospital referrals among children and it affects normal activities in school or work and needs considerable attention. Many studies have been conducted on VKC, but they provide limited epidemiological data in India. This study adds to the existing literature on VKC in India and also makes an attempt to see if PLP appears to be a consistent finding in known cases of VKC.

MATERIALS AND METHODS

An observational, cross-sectional study was conducted at a tertiary eye care center in western Maharashtra from March 2019 to February 2020. It was approved by the Institutional Ethics Committee and has been conducted in accordance with the Declaration of Helsinki. A written, informed consent was taken from all the study subjects aged more than 18 years (and from parents for those aged below 18 years). The sample size was calculated to estimate 95% confidence interval (CI) for prevalence of PLP in cases of VKC, with 5% absolute error of margin. The sample size worked out to be 152, assuming the prevalence to be 11% based on a previous study.[10]

All clinically diagnosed cases of VKC were included in the study. Allergic conjunctivitis due to atopy, contact lens–induced conjunctivitis, and any previous trauma or ocular surgery were excluded. A detailed history of all participants was taken and slit-lamp examination was performed in all cases. VKC was classified into palpebral, limbal, and mixed forms based on the presence and location of characteristic signs. The presence of cobblestone-like papillae (discrete, >1 mm with flattened-tops) involving the upper tarsal conjunctiva only, without any limbal involvement with itching sensation and/or at least one of the following symptoms, namely, photophobia, sticky mucous ropy-discharge, redness, watering, and foreign body sensation, experienced in the last six months characterized the palpebral form of VKC.[11] The limbal form included gelatinous-limbal thickening, Horner–Trantas dots (focal white limbal dots consisting of degenerated epithelial cells and eosinophils), and/or limbal inflammation with itching sensation and/or at least one of the following symptoms, namely, photophobia, sticky mucous ropy-discharge, redness, watering, and foreign body sensation experienced in the last six months.[11] The mixed form had features of both palpebral and limbal VKC. Corneal involvement with superficial punctate keratitis, corneal erosion, recurrent epithelial defect, or plaque formation (fibrin and mucous accumulation into macro-erosions) causing shield-ulcer were noted. Family history included any known allergic eye diseases, asthma, allergic rhinitis, and eczema in the family. Personal history of non-ocular allergy included any known history of allergy disease in the body not involving the eye.

Severity of the disease was graded as mild (upper tarsal papillae), moderate (Horner–Trantas dots, focal limbal inflammation <6 clock hours, limbal thickening <6 clock hours, fine punctate corneal erosions), severe (active large cobblestone appearance, coarse corneal erosions, keratitis, severe limbal inflammation in >6 clock hours), and blinding (active large cobblestone, active shield ulcer, severe annular limbal inflammation, limbal stem cell deficiency).[10,12] Presence or absence of PLP was recorded in all the cases. In the eyes with PLP, its location, extent (quadrant around the limbus; 1 quadrant = 3 clock hours), type/pattern (discrete or dot-like) and color (brown to black) were recorded.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) for Windows (version 20.0 software). Qualitative data variables were expressed as frequency and percentage while quantitative data variables were expressed as mean, SD, and median. The relation of extent of pigmentation with the severity and duration of the disease was analyzed using the Chi-squared test. A confidence level of 95% and a *P* value of less than 0.05 was considered significant.

RESULTS

A total of 152 patients of VKC who met the inclusion and exclusion criteria were part of our study. Of these, 121 (79.61%) were males (male to female ratio, 3.9:1) and the mean age at presentation was 11.4 ± 5.62 years (median, 11; range, 5–20). The maximum occurrence was in the age group of 11–15 years (32.89%) followed by the age group of 6–10 years (32.24%) [Table 1]. Seven (4.61%) patients were over the age of 20 years. Out of these seven cases, three had adult-onset of the disease (first episode at or after 20 years of age),[10] whereas the rest had continuation of

their childhood VKC beyond 20 years of age. The majority had reported in the months of May–June (59 cases; 38.82%) and least reported in the months of November–December (12 cases; 7.89%) [Figure 1]. One hundred twenty cases (79%) gave history of avoiding outdoor activities due to ocular symptoms. Seasonal exacerbations were found to be present in 112 cases (73.68%). In this study, positive family and personal history of atopy or allergic conjunctivitis was present in 19 cases (12.49%).

On analyzing symptomatology, out of all reported symptoms the most common symptom found was itching (98.68%; $P < 0.0001$), followed by redness in 78 cases (51.32%) [Table 1].

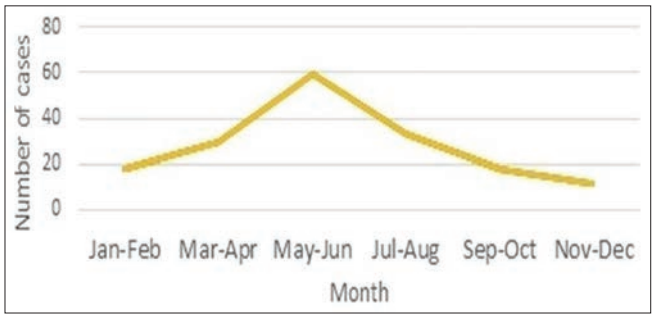


Figure 1: Seasonal distribution of patients with vernal keratoconjunctivitis

Table 1: Descriptive analysis of patients with vernal keratoconjunctivitis

History	Mean±SD || Median (Range) || Min.-Max. || Frequency (%)	
Age (Years)	11.40±5.62 || 11.00 (6.75-15.00) || 3.00-31.00	
Age		
≤5 Years	23 (15.1%)	
6-10 Years	49 (32.2%)	
11-15 Years	50 (32.9%)	
16-20 Years	23 (15.1%)	
>20 Years	7 (4.6%)	
Time Since Onset (Months)	29.99±22.83 || 24.00 (12.00-48.00) || 0.50-120.00	
Gender		
Male	121 (79.6%)	
Female	31 (20.4%)	
Laterality		
U/L	26 (17.1%)	
B/L	126 (82.9%)	
Symptoms Yes/No		
Itching	150 (98.7%)	2 (1.3%)
Redness	78 (51.3%)	74 (48.7%)
Foreign body sensation	37 (24.3%)	115 (75.7%)
Watering	52 (34.2%)	100 (65.8%)
Mucoid discharge	18 (11.8%)	134 (88.2%)
Photophobia	26 (17.1%)	126 (82.9%)
Burning sensation	6 (3.9%)	146 (96.1%)

Mixed pattern of VKC was found in 74 cases (48.68%; 95% CI 66.27–80.77%; $P < 0.58$) followed by the palpebral form [Table 2]. The most common sign found was upper tarsal papillae in 121 cases (79.61%). Limbal papillae was found in 62 cases followed by Horner–Trantas dots in 24 cases (15.74%). VKC-related complications such as superficial punctate keratopathy was noted in three cases (1.97%), limbal stem-cell deficiency (corneal neovascularization along with conjunctivalization and corneal scarring) in one case, and shield ulcer in one case. Based on the clinical scores, the overall severity of the clinical course of the disease was found to be mild in 50% of cases in our study and blinding in 1.32% of cases. Eighty-one cases showed presence of perilimbal bulbar conjunctival pigmentation (53.29%; 95% CI 45.03–61.42%; $P < 0.0001$). The pigments were multiple, scattered, mainly dot-like in appearance, and brown-black in colour. It was concentrated around the limbus and in the interpalpebral area of the bulbar conjunctiva. Among all the patients, pigmentation was mainly concentrated around the limbus and gradually faded toward the fornices. PLP was dot-like in 69 cases and discrete-type in 12 cases [Figure 2]. Table 1 shows descriptive analysis of VKC cases and Table 2 shows distribution based on type and severity of VKC and

Table 2: Distribution of patients in terms of type, severity of vernal keratoconjunctivitis, and perilimbal pigmentation

Vernal keratoconjunctivitis (VKC) Mean±SD || Median (range) || Min.-Max. || Frequency (%)	
Type Of VKC	
Mixed	74 (48.7%)
Palpebral	68 (44.7%)
Limbal	10 (6.6%)
Severity of VKC	
Mild	76 (50.0%)
Moderate	56 (36.8%)
Severe	18 (11.8%)
Blinding	2 (1.3%)
Perilimbal Pigmentation Mean±SD || Median (Range) || Min.-Max. || Frequency (%) II 95% CI	
Perilimbal pigmentation (present)	81 (53.3%); 45.1%-61.4%
Perilimbal Pigmentation Type	
Dot-like	69 (85.2%); 75.2%-91.8%
Discrete	12 (14.8%); 8.2%-24.8%
Perilimbal pigmentation colour	
Blackish	60 (96.8%); 87.8%-99.4%
Brown-black	2 (3.2%); 0.6%-12.2%
Quadrants Involved	
1 quadrant	20 (24.7%); 16.1%-35.7%
2 quadrants	31 (38.3%); 27.9%-49.8%
3 quadrants	15 (18.5%); 11.1%-29.0%
4 quadrants	15 (18.5%); 11.1%-29.0%
Extent of perilimbal pigmentation (clock hours)	5.43±3.40 || 5.00 (4.00-7.00) || 1.00-12.00

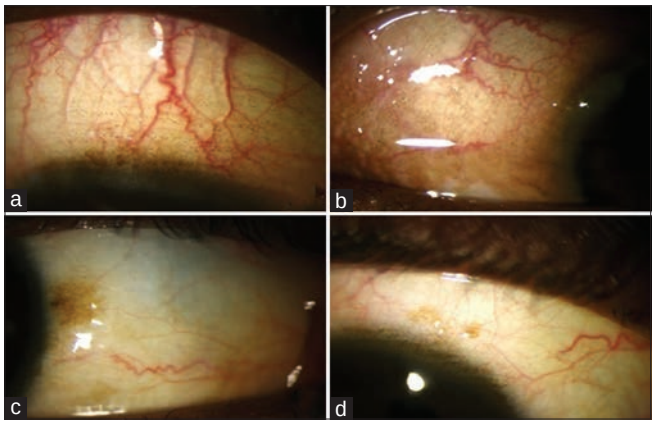


Figure 2: Types of perilimbal pigmentation (a and b) dot-like; (c and d) discrete type

presence of perilimbal pigmentation with quadrant-wise distribution. The extent of pigmentation was found to be significantly corelated to the severity of VKC ($P < 0.0001$). The extent of pigmentation increased with increasing severity of the disease. However, there was no significant correlation between the duration of the disease and the extent of perilimbal conjunctival pigmentation ($P = 0.079$).

DISCUSSION

Vernal keratoconjunctivitis (VKC) is a chronic, bilateral, ocular inflammatory disorder predominantly affecting young males. The results of our study showed that the odds of having VKC among males were 3.9 times higher than that among females. Except for one study from Nigeria, which reported female preponderance (1:1.3), many studies have reported male predominance with a male-to-female ratio of 4:1 to 2:1, which is consistent with our findings.[1,10,11–14] Multiple studies from different parts of India also support the aforementioned observation.[15–18] Previous research observed significant increase of conjunctival estrogen and progesterone receptors in children with VKC compared to healthy subjects and that activated eosinophils (EG2- positive) co-expressed the estrogen and progesterone receptors[19]; this reveals an immunoreactivity component which may be associated with hormonal factors. It has also been found that VKC cases have different circulating sex-hormone levels compared to normal cases, which suggest a role of sex hormones in the pathogenesis of this disease.[20] The mean age at presentation was 11 ± 5.62 years in our study, with a majority of the patients belonging to the age group of 11–15 years. This is in accordance with various Indian studies that have reported higher incidence of VKC in a similar age group.[10,17,21–24] In contrast to this, a study from eastern India reported a much younger age group (5–9 years) with VKC.[16]

The onset of VKC is usually after the age of five years and the condition commonly resolves around puberty. However, it is also reported in adults aged >20 years with an incidence ranging from 3% to 6%.[1,23] Different environmental factors may be responsible for this varied demography. Children with VKC tend to avoid sunlight exposure and outdoor activities during summer and spring. In our study, 79% of cases gave history of avoiding outdoor activities due to ocular symptoms. This may be due to the exacerbation of symptoms like itching, redness, and photophobia while playing outdoor games in hot and humid weather. This is in lieu of India being a tropical country and VKC having its higher incidence in tropical areas than temperate areas. VKC has seasonal exacerbations; however, its chronic perennial form has also been described in the literature. In this study, 40 patients (26.31%) had chronic perennial disease. This is less than the number of cases reported in recent Indian studies, which reported 60% of cases with perennial disease and only 35% with seasonal exacerbations.[25] However, seasonal variations have been seen in multiple studies including ours. VKC cases attended the out-patient department almost throughout the year, but with a greater incidence in the months of May to June and with a drastic decline during winter season. It is in consonance with most studies that state that VKC is more prevalent in hot and dry weather.[10,16,26]

The immunopathogenesis of VKC is multifactorial and has more environmental causes. Classically it has been thought of as a type I IgE-mediated hypersensitivity reaction, though it is accepted that there is cell-mediated involvement also. In our study, 12.49% of cases had family or personal history in some form of ocular or non-ocular allergies. Of this, family history of non-ocular allergies such as episodes of asthma, rhinitis, or eczema was seen in 7.23% of cases. Previous Indian studies reported 4.9%–5.8% of cases with history of allergy.[10,18] But this is in contrast to other studies that found approximately one-third of cases to be atopic based on the history of hay fever, asthma, eczema, etc.[17,27,28] Different environmental factors might be associated with the same disease and responsible for these heterogenous results.

The predominant form found was mixed form of VKC in 48.68% of cases followed by palpebral (44.74%) and limbal forms (6.58%). It is in agreement with the studies done in Ethiopia (53%) and Egypt (70%) which reported mixed form as the most common presentation.[28] In contrast to this, a few studies from Nigeria (47%) and Mali (65%) reported the palpebral form as the most common.[29,30] Palpebral forms are said to be more prevalent in Europe and America, whereas the mixed and limbal forms are more commonly seen in Asia and Africa, respectively, with some geographic variations and probably due to hospital attending bias. Various Indian studies are in line with our observation of mixed form being

the most common form of VKC,[10,18,24] whereas a few studies varied from our results and have reported the palpebral form[15,17] or the limbal form as being the most common.[16] Even though the reason behind this varied pattern is not clear, this disparity might be in view of different study populations, study designs, and study periods.

Vernal conjunctivitis has a varied spectrum of presentation, from itching, ropy discharge, redness, watering to severe forms of corneal ulcer leading to loss of vision. In our study, the most common presenting symptom was itching (98.68%) which supports the dictum, "no itching, no vernal/spring catarrh" in VKC.[15–17,23,24] Our study corroborated the information that upper tarsal papillae (UTP) (79.61%) was the most common sign seen in VKC. This was followed by the presence of limbal thickening in 40.79% of cases. This finding was consistent with previous studies from Nigeria and Italy.[25,29] Except for one Indian study,[21] which reported conjunctival congestion as the most common sign, others have shown UTP as the most common sign.[15,17,18,23,24] The corneal involvement in VKC is due to the combined effect of mechanical injury by the friction of giant papillae over the cornea and release of inflammatory mediators from activated eosinophils and mast cells in the conjunctiva; this can result in the formation of shield ulcers. In our study, only one case of shield ulcer was present involving the upper temporal quadrant of the cornea which was managed with debridement, supratarsal triamcinolone injection, and bandage contact lens with good recovery [Figure 3]. Fewer severe cases may be contributed by the fact that a majority of the patients reported in their early stage of the disease and managed the disease on time.

PLP is a new clinical sign described in VKC in recent years.[7,8] The role of type I hypersensitivity reaction in VKC has been supported by various studies revealing elevated tear histamine levels and clinical response to mast-cell stabilizers. On the other hand, immunohistochemical studies showed the presence of T-helper cells which indicate the role of type IV immune response as well.[25] The limbus is actively involved in the process of immunological reaction as it is rich in Langerhans cells (macrophages) which act as antigen-presenting cells in the eye, mast cells, and melanocytes. Rao and Padmanabhan[7] suggested that the presence of PLP may be a result of the ocular surface changes reflecting immune response and was described as a consistent finding in VKC.[8] It was followed by another study from Hong Kong in Chinese population in which this pigmentation was reported in all the cases. Subsequently, multiple Indian studies from various parts have reported this new emerging clinical sign, ranging from 8% tp 11%.[5,10,24] In contrast, we have observed a higher incidence (53.29%) of PLP in cases of VKC. This was noted as multiple, scattered, dot-like pigmentation with varying colour from light to dark-brown. We had a larger number of patients with this sign and thus, it could be a consistent finding in VKC.

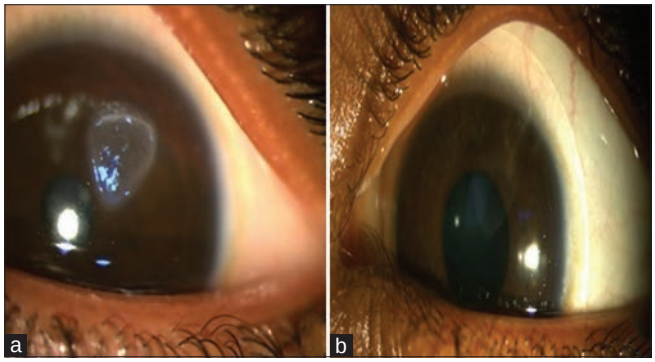


Figure 3: (a) Shield ulcer; (b) Resolved shield ulcer with bandage contact lens *in situ*

In our study, the overall severity of the clinical course of the disease was found to be mild, seen in 50% of cases.[10,17] The presence of PLP was found to occur in all the grades of VKC. The extent of pigmentation was found to be significantly corelated with the severity of VKC. However, there was no statistically significant correlation seen between duration of the disease and extent of perilimbal conjunctival pigmentation. Similarly, no relation was found between age and severity of inflammation; and this PLP was present even when the disease went into remission. Our study focused on clinical presentation of known cases of VKC in western India and adds to the existing limited epidemiological data from India. It also reports a higher incidence of PLP which appears to be an early and a consistent finding with VKC. To the best of my knowledge, this is the first study to corelate presence of PLP in detail in cases of VKC.

CONCLUSION

The clinical profile of VKC seen in the tropical climate of India is similar to that seen in other countries. The distinct feature of chronic perennial form, early presentation, and higher incidence of presence of perilimbal pigmentation may be a useful diagnostic sign in VKC patients with early disease. This knowledge will help in early diagnosis, timely management of VKC by ophthalmologists and in preventing sight-threatening complications, thereby providing good quality of life to young population.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other

clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Leonardi A, Busca F, Motterle L, Cavarzeran F, Fregona IA, Plebani M, *et al*. Case series of 406 vernal keratoconjunctivitis patients: A demographic and epidemiological study. Acta Ophthalmol Scand 2006;84:406-10.
2. Ono SJ, Abelson MB. Allergic conjunctivitis: Update on pathophysiology and prospects for future treatment. J Allergy Clin Immunol 2005;115:118-22.
3. De Smedt S, Wildner G, Kestelyn P. Vernal keratoconjunctivitis: An update. Br J Ophthalmol 2013;97:9-14.
4. Uchio E, Kimura R, Migita H, Kozawa M, Kadonosono K. Demographic aspects of allergic ocular diseases and evaluation of new criteria for clinical assessment of ocular allergy. Graefes Arch Clin Exp Ophthalmol 2008;246:291-6.
5. Tanaka M, Dogru M, Takano Y, Miyake-Kashima M, Asano-Kato N, Fukagawa K, *et al*. The relation of conjunctival and corneal findings in severe ocular allergies. Cornea 2004;23:464-7.
6. Albert DM, Jakobiec FA. Principle and Practices of Opthalmology. 2nd ed. United States of America: W.B. Saunders Company; 2000.
7. Rao SK, Padmanabhan P. Perilimbal conjunctival pigmentation in vernal conjunctivitis: A new sign. Cornea 2002;21:432.
8. Rao SK, Meenakshi S, Srinivasan B, Baluswamy S. Perilimbal bulbar conjunctival pigmentation in vernal conjunctivitis: A prospective evaluation of a new clinical sign in an Indian population. Cornea 2004;23:356-9.
9. Leonardi A. Vernal keratoconjunctivitis: Pathogenesis and treatment. Prog Retin Eye Res 2002;21:319-39.
10. Saboo US, Jain M, Reddy JC. Demographic and clinical profile of vernal keratoconjunctivitis at a tertiary eye care centre in India. Indian J Ophthalmol 2013;61:486-9.
11. Ashwini K, Dhatri K, Rajeev K. Vernal keratoconjunctivitis in school children in north Bangalore: An epidemiological and clinical evaluation. J Evol Med Dent Sci 2015;4:15070-6.
12. Bonini S, Sacchetti M, Mantelli F, Lambiase A. Clinical grading of vernal keratoconjunctivitis. Curr Opin Allergy Clin Immunol 2007;7:436-41.
13. Ukponmwan CU. Vernal conjunctivitis in Nigerians: 109 consecutive cases. Trop Doct 2003;33:242-5.
14. Nebbioso M, Zicari AM, Celani C, Lollobrigida V, Grenga R, Duse M. Pathogenesis of vernal keratoconjunctivitis and associated factors. Semin Ophthalmol 2015;30:340-4.
15. Sharma P, Aggarwal S, Joy J, Naimi S. Study of clinical profile of vernal keratoconjunctivitis in Ghaziabad. J Evid Based Med Healthc 2019.
16. Adhikari S, Naskar AK, Kabasi S, Deb S, Deb RK, Sen S. A clinicopathological study of vernal conjunctivitis in urban and rural areas of Eastern India: A hospital based study. Int J Res Med Sci 2018;6:966-73.
17. Rajasekar K. A clinical study on aetiopathogenesis, course and presentation of vernal keratoconjunctivitis seeking tertiary eye care in Chennai. J Evid Based Med Healthc 2018;5:2264-7.
18. Sethi M, Nanda R, Bali A, Sadhotra P. Hospital based study of demography and clinical picture of vernal keratoconjunctivitis. Int J Res Med Sci 2017;6:65.
19. Bonini S, Lambiase A, Schiavone M, Centofanti M, Palma LA, Bonini S. Estrogen and progesterone receptors in vernal keratoconjunctivitis. Ophthalmology 1995;102:1374-9.
20. Sacchetti M, Lambiase A, Moretti C, Mantelli F, Bonini S. Sex hormones in allergic conjunctivitis: Altered levels of circulating androgens and estrogens in children and adolescents with vernal keratoconjunctivitis. J Immunol Res 2015;2015:945317.
21. Padha A, Qayum S. Clinical profile of VKC patients presenting at a tertiary care hospital in Rajouri, J&K, India. Glob J Res Anal 2019;8:3-4.
22. Nagpal H, Rani N, Kaur M. A retrospective study about clinical profile of vernal keratoconjunctivitis patients at a tertiary care hospital in Patiala, Punjab, India. Kerala J Ophthalmol 2017;29:189-91.
23. Siddegowda S, Venkataramana PA, Manjunath SA. Demography, clinical profile and compliance of patients of vernal keratoconjunctivitis in a tertiary eye care centre in Southern Karnataka. Indian J Clin Exp Ophthalmol 2020;6:69-73.
24. Jivangi VS, Raikar HA, Khatib ZI, Abhilasha MN, Suhana A. Clinical profile of patients with vernal keratoconjunctivitis. Int J Res Med Sci 2015;3:2831-4.
25. Pucci N, Novembre E, Lombardi E, Cianferoni A, Bernardini R, Massai C, *et al*. Atopy and serum eosinophil cationic protein in 110 white children with vernal keratoconjunctivitis: Differences between tarsal and limbal forms. Clin Exp Allergy 2003;33:325-30.
26. Malu KN. Vernal keratoconjunctivitis in Jos, North-central Nigeria: A hospital based study. Sahel Med J 2014;17:65-70.
27. Bonini S, Bonini S, Lambiase A, Marchi S, Pasqualetti P, Zuccaro O, *et al*. Vernal keratoconjunctivitis revisited: A case series of 195 patients with long-term followup. Ophthalmology 2000;107:1157-63.
28. Marey HM, Mandour SS, El Morsy OA, Farahat HG, Shokry SM. Impact of vernal keratoconjunctivitis on school children in Egypt. Semin Ophthalmol 2017;32:543-9.
29. Duke RE, Odey F, De Smedt S. Vernal keratoconjunctivitis in public primary school children in Nigeria: Prevalence and nomenclature. Epidemiol Res Int 2016;2016:9854062.
30. Thera JP, Hughes D, Tinley C, Bamani S, Traore L. Magnitude of vernal kerato conjunctivitis among school children in Koulikoro. Scholars J Appl Med Sci 2016;4:180-2.

Original Article

Evaluation of tacrolimus and cyclosporine in the treatment of vernal keratoconjunctivitis in children

ABSTRACT

Aims: To compare the efficacy and safety of 0.03% tacrolimus eye ointment with 2% cyclosporine eye drops in the treatment of vernal keratoconjunctivitis. **Settings and Design:** Comparative, Hospital-based, Prospective, Randomized, Clinical study. **Methods and Material:** About 56 children diagnosed with Vernal keratoconjunctivitis (VKC) were enrolled in the study. All the subjects underwent a comprehensive ophthalmic evaluation. Total subjective symptom scoring (TSSS) and Total objective sign scoring (TOSS) were done for each patient based on their history and clinical examination. They were divided into two groups. One group was treated with 0.03% tacrolimus ointment bd and the other with 2% cyclosporine eye drops tid. Both groups were also put on carboxymethylcellulose eye drops four times a day. Steroids were never used during the study. The patients were followed up at intervals of two weeks, four weeks, and eight weeks. At each follow-up, the TSSS and TOSS were done for each patient. Patients were also questioned about any adverse effects encountered by them during the treatment. A comparison was done between both groups based on the above scoring. **Results:** There was progressive reduction which was statistically significant ($P < 0.05$) in the TSSS and TOSS in both the groups throughout treatment. Reduction in TSSS The only adverse effect reported by a few patients was a burning sensation that was not severe enough to discontinue treatment. **Conclusions:** Both tacrolimus 0.03% eye ointment and cyclosporine 2% eye drops are effective in the treatment of VKC without any significant severe side effects. Tacrolimus eye ointment was more effective than cyclosporine drops.

Keywords: Cyclosporine, tacrolimus, vernal keratoconjunctivitis

INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a chronic, bilateral, conjunctival inflammatory condition found in individuals predisposed to their atopic background. The onset of the disease is generally below age 10, lasts for 2 to 10 years, and usually resolves during late puberty. Young males in dry, hot climates are those who are primarily affected.[1]

Steroid drops are the most effective medication available but are also the most unsafe, especially with chronic and unmonitored usage.[2] Its long-term use is associated with complications such as cataracts and glaucoma. VKC in warm temperature zones is associated with a chronic course that warrants a longer duration of therapy.[3] Thus, there is a need for developing better management strategies for these patients.

Submitted: 09-Mar-2022 **Revised:** 05-Sep-2022
Accepted: 05-Oct-2022 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	Quick Response Code
DOI: 10.4103/kjo.kjo_46_22	

Immunomodulatory drugs like Cyclosporine and Tacrolimus have achieved breakthrough results in the treatment of severe allergic eye diseases, and are well tolerated with negligible side effects according to many recent studies. Cyclosporine eye drops were found to be effective in treating severe VKC and Tacrolimus ointment has shown satisfactory results in the treatment of recalcitrant VKC.[4] Both these drugs prevent the activation of T cells by inhibiting Calcineurin. Calcineurin is a serine/threonine phosphatase enzyme which is required for the expression of many cytokines and costimulatory molecules necessary for the activation of T cells.[5]

Suresha A. R, Gaargi Shashidhar, Prabhudeva H
Department of Ophthalmology, J.J.M. Medical College, Davanagere, Karnataka, India

Address for correspondence: Dr. Gaargi Shashidhar, Department of Ophthalmology, J.J.M. Medical College, Davanagere, Karnataka, India.
E-mail: gaargis@yahoo.co.in

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Suresha AR, Shashidhar G, Prabhudeva H. Evaluation of tacrolimus and cyclosporine in the treatment of vernal keratoconjunctivitis in children. Kerala J Ophthalmol 2023;35:155-60.

This study aims to compare the efficacy and safety of 0.03% tacrolimus eye ointment with 2% cyclosporine eye drops in the treatment of vernal keratoconjunctivitis.

SUBJECTS AND METHODS

A prospective, randomized, comparative, clinical study was conducted after taking clearance from the institutional ethical committee. About 56 children attending the ophthalmology Outpatient department (OPD) who were diagnosed with VKC with no previous treatment, or previous history of treatment with antiallergic drugs who were symptomatic, were enrolled in the study. Children with other ocular diseases like uveitis, corneal degenerations/dystrophies/opacities/infections, strabismus, subluxated or dislocated lens, glaucoma, and previous ocular surgeries were excluded. Patients with a history of use of steroids were also not considered for the study.

A detailed history including age at onset of disease, duration of illness, history of medications used earlier, family history of the same illness, and any other illness associated with VKC such as allergic rhinitis or dermatitis was taken. The subjective symptoms of the patients and the objective signs noted on examination were graded as follows according to the following Clinical scoring system by Bliek *et al*.[6]

Grading of Symptoms: Symptoms considered included Itching, tearing, photophobia, discharge, and foreign body sensation

- 0: Indicating no symptoms
- 1+: Mild symptoms of discomfort which were just noticeable
- 2+: Moderate discomfort noticed most of the day but did not interfere with daily routine activities
- 3+: Severe symptoms interfering with daily routine activities

Grading of Signs: It was done considering the following signs:-

Each patient's total subjective symptom score (TSSS) and total objective sign score (TOSS) were calculated based on the above grading.

Patients were divided into 2 groups I and II. Group I was requested to use 0.03% tacrolimus eye ointment twice daily and Group II was requested to use 2% cyclosporine eye drops 3 times daily. Both the groups were also advised cold compression and the use of lubricating eye drops (0.5% carboxymethylcellulose) 4 times daily. A complete ophthalmologic assessment was done again at 2 weeks, 4 weeks, and 8 weeks. During follow-up visits, all patients were evaluated for improvement in subjective symptoms, and objective signs. Scoring (TSSS and TOSS) was done as mentioned above in each of the follow-up visits. Patients were also questioned about any adverse effects encountered by them during the treatment. The two groups were assessed and a comparison was done between both groups based on the above scoring.

RESULTS

A total of 56 patients were enrolled in the study consisting of 29 patients in the Tacrolimus group and 27 patients in the Cyclosporine group. Descriptive statistics of the explanatory and outcome variables were calculated by the mean, standard deviation for quantitative variables, frequency, and proportions for qualitative variables. Inferential statistics like the Chi-square test was used for qualitative variables, independent sample *t*-test was applied to compare the quantitative variables between the groups. Repeated measures ANOVA was applied to compare the quantitative within the group at different time intervals with posthoc Bonferroni for comparison between two-time intervals. The level of significance was set at 5%.

The distribution of VKC cases in different age groups and the descriptive statistics on age in these cases are presented in Table 1. The majority of VKC cases were seen in the 6–10 years group (39.3%), followed by the 1–5 years group (26.8%). The above 15 years group constituted 8.9% of the VKC cases. 67.9% of the subjects were male and 32.1% were female. There was a statistically significant difference noted between the two groups in terms of gender distribution.

There was no statistically significant difference in the treatment history between the groups. Only 2 subjects had a family history of VKC. 3.6% of subjects had associated allergic dermatitis and 16.1% had associated allergic rhinitis. 80.4% of subjects did not have any other associated systemic conditions. The most common type was the mixed

Grade	Bulbar Conjunctival Hyperemia	Palpebral conjunctival papillary hypertrophy	Punctate keratitis	Tranta's dots	Limbal infiltration
0	No	No	Absent	No dots	Absent
1+	Mild	Mild	One Quadrant	1-2 dots	<90°
2+	Moderate	Moderate (hazy view of the deep tarsal vessels)	Two Quadrants	3-4 dots	>90° but <180°
3+	Severe	Severe (deep tarsal vessels not visible in >50% of the surface)	Three or more Quadrants	>4 dots	>180°

Table 1: Comparison of the parameters within the groups between two time intervals using the chi-square test

Parameter	Groups		Total	Chi-square value	*P*
	Tacrolimus	Cyclosporine			
Age (yrs)					
3-5	9 (31.0%)	5 (18.5%)	14 (25%)	1.52	0.67
6-10	10 (34.5%)	12 (44.4%)	22 (39.3%)		
11-15	7 (24.1%)	8 (29.6%)	15 (26.8%)		
>15	3 (10.3%)	2 (7.4%)	5 (8.9%)		
Gender					
Females	5 (17.2%)	13 (48.1%)	18 (32.1%)	6.12	0.013
Males	24 (82.8%)	14 (51.9%)	38 (67.9%)		
Treatment History					
Previously on treatment	13 (44.8%)	10 (37%)	23 (41.1%)	0.35	0.55
Nil	16 (55.2%)	17 (63.0%)	33 (58.9%)		
Family History					
Present	2 (6.9%)	0 (0.0%)	2 (3.6%)	1.93	0.16
Nil	27 (93.1%)	27 (100%)	54 (96.4%)		
Other Associated History					
Dermatitis	0 (0.0%)	2 (7.4%)	2 (3.6%)	2.24	0.32
Rhinitis	5 (17.2%)	4 (14.8%)	9 (16.1%)		
Nil	24 (82.8%)	21 (77.8%)	45 (80.4%)		
Type of VKC					
Bulbar	10 (34.5%)	6 (22.2%)	16 (28.6%)	5.93	0.051
Palpebral	4 (13.8%)	0 (0.0%)	4 (7.1%)		
Mixed	15 (51.7%)	21 (77.8%)	36 (64.3%)		

Table 2: comparison of the parameters within the groups between two time intervals using post-hoc bonferroni test

Parameters	Groups	First visit v/s 2 weeks	First visit v/s 4 weeks	First visit v/s 8 weeks	2 weeks v/s 4 weeks	2 weeks v/s 8 weeks	4 weeks v/s 8 weeks
TSSS	Tacrolimus						
	Mean diff	0.759	1.345	2.241	0.586	1.483	0.897
	P	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*
	Cyclosporine						
	Mean diff	0.231	0.923	1.769	0.692	1.538	0.846
	P	0.067	0.000*	0.000*	0.000*	0.000*	0.000*
TOSS	Tacrolimus						
	Mean diff	2.207	3.862	5.345	1.655	3.138	1.483
	P	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*
	Cyclosporine						
	Mean diff	1.885	3.308	5.000	1.423	3.115	1.692
	P	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*
IOP (RE)	Tacrolimus						
	Mean diff	-0.207	-0.276	-0.172	-0.069	0.034	0.103
	P	1.000	1.000	1.000	1.000	1.000	1.000
	Cyclosporine						
	Mean diff	0.308	0.000	0.231	-0.308	-0.077	0.231
	P	1.000	1.000	1.000	1.000	1.000	1.000
IOP (LE)	Tacrolimus						
	Mean diff	-0.172	0.034	-0.034	0.207	0.138	-0.069
	P	1.000	1.000	1.000	1.000	1.000	1.000
	Cyclosporine						
	Mean diff	0.077	0.000	0.231	-0.077	0.154	0.231
	P	1.000	1.000	1.000	1.000	1.000	1.000

type (64.3%) followed by the bulbar (28.6%) and then the palpebral type (7.1%). [Table 2].

The mean TSSS was 2.90 + 0.41 in the Tacrolimus group and 2.74 + 0.59 in the Cyclosporine group at the time of

Table 3: Distribution of the subjects based on adverse effects at 2, 4, and 8 weeks

Side effects	Groups		Total	Chi-square value	*P*
	Tacrolimus	Cyclosporine			
2 weeks					
Burning Sensation	1 (3.40%)	2 (7.40%)	3 (5.40%)	0.43	0.51
Nil	28 (96.60%)	25 (92.60%)	53 (94.60%)		
4 weeks					
Burning Sensation	0 (0.0%)	1 (3.7%)	1 (1.8%)	1.09	0.29
NIL	29 (100.0%)	26 (96.3%)	55 (98.2%)		
8 weeks					
Burning Sensation	0 (0.0%)	1 (3.7%)	1 (1.8%)	1.09	0.29
NIL	29 (100.0%)	26 (96.3%)	55 (98.2%)		

initial presentation. The TOSS was found to be 6.24 + 1.33 and 6.37 + 1.47 in the Tacrolimus and Cyclosporine groups respectively. There was no statistically significant difference between both groups ($P > 0.05$). At 2 weeks, a statistically significant difference ($P = 0.008$) was noted between the TSSS of the Tacrolimus (2.14 + 0.35) and Cyclosporine (2.52 + 0.64). However, no significant difference was noted in the TOSS between both groups at 2 weeks [Graphs 1 and 2].

There was a progressive reduction in the TSSS and TOSS in both groups throughout treatment. The reduction in the scores was statistically significant in both groups. [Table 2] In the Tacrolimus group, 37.9% of patients were symptom-free and 20.7% of patients did not have any signs at the end of 8 weeks. In the Cyclosporine group, 11.5% of patients were symptom-free and did not have any signs of VKC at the end of 8 weeks.

Burning Sensation was the only adverse effect reported by 5.4% of patients at 2 weeks and 1.8% of patients at 4 and 8 weeks of follow-up. [Table 3] This was not found to be statistically significant. It was not severe enough to discontinue treatment. No significant difference was found in the IOP values in both groups at follow-up periods when compared to the baseline values.

DISCUSSION

The patients included in this study comprised children with ages ranging from 3 to 17 years. The majority of VKC cases were seen in the 6–10 years group (39.3%). This was followed by the age group of 11–15 years (26.8%), 3–5 years (25%), and above the age of 15 years (8.9%). The youngest patient in this study was 3 years old, while the oldest was 17 years old. This study's findings as far as the age of occurrence and distribution of VKC cases in different age groups is in concordance with such studies done in other parts of the world as shown below.

Age group	Our study	Leonardi *et al.*[7]	Al-Akily SA *et al.*[8]	Siddegowda *et al.*[9]	Sinha *et al.*[10]
0-5 years	25%	31.8%	7.42%	23%	6.66%
6-10 years	39.3%	56.3%	41.8%	42%	50%
11-15 years	26.8%	35.1%	33.4%	27%	29.16%
>15 years	8.9%	2.4%	17.4%	8%	14.2%

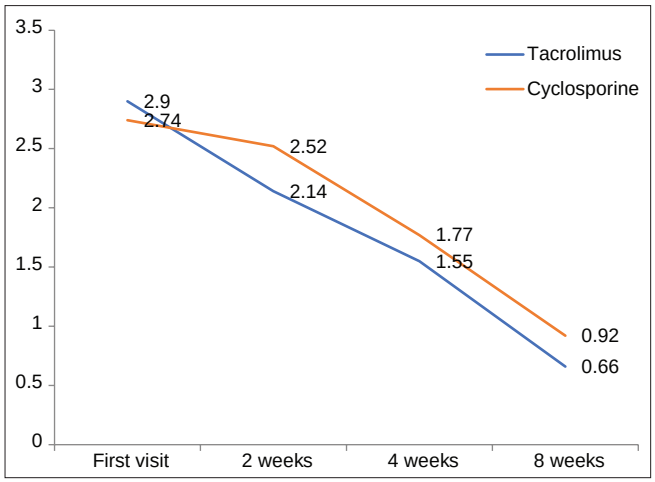
Among the patients included in our study, 38 were male (67.9%), and 18 were female (32.1%). Males were found to be affected more than females with a male: Female ratio of 2.1:1. In other studies also, it has been found that VKC is more common in males, with the male-to-female ratio in different studies varying from 4:1 to 2:1. This has been shown below.

	Our study	Leonardi *et al.*[7]	Al-Akily SA *et al.*[8]	Siddegowda *et al.*[9]	Ramzan *et al.*[11]
Males	67.9%	76.6%	75.8%	67%	72%
Females	32.1%	23.4%	24.2%	33%	28%
Male: Female ratio	2.1: 1	3.3: 1	3.1: 1	2: 1	2.6: 1

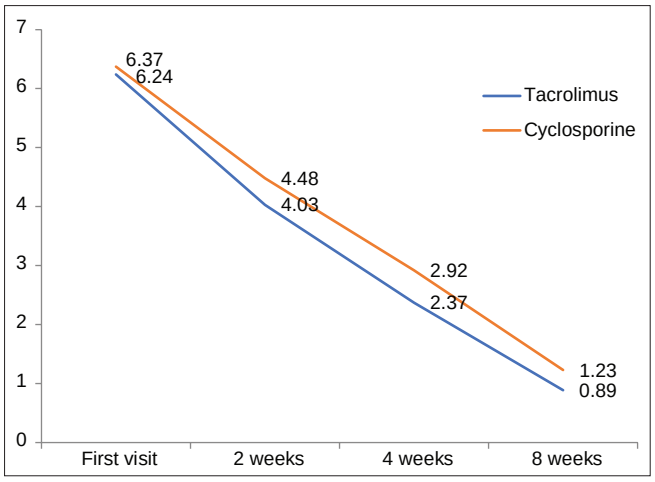
A total of 41.1% of patients enrolled in our study had a history of treatment with anti-allergic medications and/or tear substitutes. Those patients who had a history of steroid use were not enrolled in the study.

2 patients (3.6%) gave a positive family history of VKC in our study. A similar result was obtained in a study by Singla *et al.*[12] where positive family history was seen in 2 out of 56 patients (3.6%). Saboo *et al.*[13] also noted a positive family history in only 4.91% of patients. Positive family history is seen more commonly in temperate regions when compared to tropical areas.

About 2 patients (3.6%) gave a history of associated allergic dermatitis and 9 patients (16.1%) gave a history of allergic rhinitis in this study. Singla *et al.*[12] also reported a history of allergic dermatitis in 5.4% and allergic rhinitis in 19.6%. In the study by Saboo *et al.*[13] out of 468 patients, 5 (1%) had associated allergic dermatitis, while 15 patients (3.2%) had a history of concomitant allergic respiratory disorders. The higher percentage in our study is probably due to the smaller sample size.



Graph 1: Comparison of tsss within the groups at different time intervals



Graph 2: Comparison of toss within the groups at different time intervals

The most common clinical type of VKC in our study was the mixed type (64.3%) followed by the bulbar (28.6%) and then the palpebral type (7.1%). A comparison with other studies is shown below.

Type of VKC	Our Study	Saboo *et al.*[13]	Siddegowda *et al.*[9]	Al-Akily SA *et al.*[8]
Bulbar	28.6%	12.6%	18%	48%
Palpebral	7.1%	15.6%	16%	34.1%
Mixed	64.3%	72.2%	66%	17.9%

The baseline Total Subjective Symptom Score (TSSS) and Total Objective Sign Score (TOSS) in both Tacrolimus and Cyclosporine groups were comparable at the time of presentation. Significant reductions in TSSS and TOSS were noted at follow-up visits in both groups.

At the 2-week follow-up visit, a significant difference was noted between the reduction of symptoms in the Tacrolimus vs the Cyclosporine group. The Tacrolimus group showed a greater reduction in the TSSS when compared to the Cyclosporine group. However, no significant difference was noted in the TOSS between both groups at 2 weeks. Also, at the end of 8 weeks, a greater percentage of patients were symptom-free (37.9%) and sign-free (20.7%) in the Tacrolimus group when compared to the cyclosporine group (11.5%).

Labcharoenwongs *et al.*[14] also conducted a similar study to compare 0.1% Tacrolimus ointment and 2% cyclosporine eye drops in the treatment of VKC. They followed up with patients at 1, 4, 8, and 12 weeks after starting treatment. They also reported that patients in both groups showed a significant reduction in TSSS and TOSS when compared to baseline at 4 and 8 weeks. Response to Tacrolimus ointment could be observed as early as after one week of treatment with continued improvement throughout the study period. However, the response to cyclosporine treatment was noticeable after 2 weeks. They also reported that symptoms and signs were more improved with Tacrolimus than cyclosporine at the end of the study period, albeit not statistically significant.

In the study by Choudhary P, *et al.*[15] Total subjective symptom score (TSSS) at final evaluation (mean change from baseline to 8 weeks), improvement was 5.2% more in the tacrolimus group (83.7%) than cyclosporine group (78.5%). Total ocular sign scores (TOSS) final evaluation (mean change from baseline to 8 weeks), improvement was 11.6% more in the tacrolimus group (81.6%) than cyclosporine group (70.0%). The findings of these two studies are like those of our study.

Singla *et al.*[12] their study compared 0.1% Tacrolimus eye ointment used bd with 2% cyclosporine drops used 4 times a day. In their study, both 0.1% Tacrolimus and 2% Cyclosporine cause a reduction in TSSS and TOSS from the 4th week onwards. Early effects of tacrolimus and cyclosporine have not been reported. Both drugs were found to be equally effective and safe in VKC. A similar prospective, double-masked, randomized comparative study was conducted by Rashmi Kumari *et al.*[4] in 2016 in which 19 patients received 0.03% Tacrolimus eye ointment daily for 6 weeks and the other 15 received 0.05% Cyclosporine eye drops four times daily for 6 weeks. There was a reduction in TSSS and TOSS in both groups from 2 weeks onwards. But the difference between the two groups ($P = 0.54$) was not significant. This study reported that tacrolimus brought about an improvement in the signs and symptoms of VKC similar to that of cyclosporine A.

The difference in efficacy of tacrolimus and cyclosporine in the above publications can be due to a lack of early follow-up, differences in methods for drug preparation, and due to differences in disease severity among patients recruited in different studies.

Burning Sensation was the only adverse effect reported by 5.4% of patients at 2 weeks and 1.8% of patients at 4 and 8 weeks of follow up which was not statistically significant. It was not severe enough for any patient to discontinue treatment. At all points of treatment IOP, lens and fundus remained within normal limits in our patients.

CONCLUSION

Both 2% cyclosporine eye drops and 0.03% Tacrolimus eye ointment were found to be efficacious in the treatment of VKC and safe for use in children in the age group of 3 to 17 years. 0.03% Tacrolimus ointment was found to give an early reduction in symptoms during the disease within the first 2 weeks. It was also found to be slightly better than 2% cyclosporine drops in providing relief from symptoms and signs at the end of the study period. Tolerability to both drugs was good with minimal side effects. Hence, both drugs have equal potential to be used as first-line drugs in vernal keratoconjunctivitis.

Limitations

In this study, we did not consider a placebo group which may have led to statistical errors. Also, blinding was not done. The recurrence of disease following discontinuation of medication has also not been taken into consideration due to the short duration of the study. Larger multicenter studies with bigger sample sizes need to be conducted to confirm and add to the above results.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Krachmer J, Mannis M, Holland E. Cornea. Philadelphia: Elsevier/ Mosby; 2005.
2. Gokhale NS. Systematic approach to managing vernal keratoconjunctivitis in clinical practice: Severity grading system and a treatment algorithm. Indian J Ophthalmol 2016;64:145-8.
3. Samyukta SK, Pawar N, Ravindran M, Allapitchai F, Rengappa R. Monotherapy of topical tacrolimus 0.03% in the treatment of vernal keratoconjunctivitis in the pediatric population. J AAPOS 2019;23:36. e1-36.e5.
4. Kumari R, Saha B, Sinha BC, Mohan N. Tacrolimus versus Cyclosporine- Comparative Evaluation as First line drug in Vernal keratoconjuctivitis. Nepal J Ophthalmol 2017;9:128-35.
5. Azzi JR, Sayegh MS, Mallat SG. Calcineurin inhibitors: 40 years later, can't live without. J Immunol 2013;191:5785-91.
6. Bliek JH, Tabbara KF. Topical cyclosporine in vernal keratoconjunctivitis. Ophthalmology 1991;98:1679-84.
7. Leonardi A, Busca F, Motterle L, Cavarzeran F, Fregona IA, Plebani M, *et al*. Case series of 406 vernal keratoconjunctivitis patients: A demographic and epidemiological study. Acta Ophthalmol Scand 2006;84:406-10.
8. Al-Akily SA, Bamashmus MA. Ocular complications of severe Vernal keratoconjunctivitis (VKC) in Yemen. Saudi J Ophthalmol 2011;25:291-4.
9. Siddegowda S, Venkataramana PA, Manjunath SA. Demography, clinical profile and compliance of patients of vernal keratoconjunctivitis in a tertiary eye care centre in Southern Karnataka. Indian J Clin Exp Ophthalmol 2020;6:69-73.
10. Sinha R, Bhaskar G, Ali MS, Ambastha A, Aayushi. Demography and clinical profile of patients of vernal keratoconjunctivitis in a tertiary eye care center of Bihar. IP Int J Ocul Oncol Oculoplasty 2019;5:90-3.
11. Ramzan R, Vakil AA, Rashid S. To study the clinical profile of patients of vernal keratoconjunctivitis in Kashmir Valley. Int J Health Sci Res 2021;9.
12. Singla E, Singh H, Kaur, Walia S. A double-masked comparison of 0.1% tacrolimus ointment and 2% cyclosporine eye drops as first line drugs in the treatment of vernal keratoconjunctivitis. IOSR J Dent Med Sci 2017;16:30-5.
13. Saboo US, Jain M, Reddy JC, Sangwan VS. Demographic and clinical profile of vernal keratoconjunctivitis at a tertiary eye care center in India. Indian J Ophthalmol 2013;61:486-9.
14. Labcharoenwongs P, Durongpisitkul W, Dumrongkigchaiporn P, Jirapongsananuruk O, Visitsunthorn N, Kosrirukvongs P, *et al*. A double- 93 blind comparison of efficacy of 0.1% tacrolimus ophthalmic ointment and 2% cyclosporine eye drop vernal keratoconjunctivitis. J Allergy Clin Immunol 2006;117:S168.
15. Choudhary P, Singh SK, Chaurasia RC, Jindal M. A prospective study to compare the efficacy of tacrolimus vs cyclosporine in vernal keratoconjunctivitis in children in India. Int J Basic Clin Pharmacol 2019;8:1297.

Original Article

Parents' perception about children screen time and myopia during covid-19 pandemic

ABSTRACT

Purpose: To understand parents' perception of children's screen time and myopia during the COVID-19 pandemic. **Methods:** In this e-survey, 413 parents were included. It was designed on the "Google Forms website and distributed through the social media platform." The information was collected regarding parent perception of children's screen use and time spent on digital devices during and after the post-COVID-19 pandemic and knowledge about myopia. The statistical analysis was carried out using SPSS. **Results:** In this study, 56 children were myopic according to parental responses. The majority of the parents reported their child is spending more time watching television (73%) and using smartphones (79%) which included playing video/online games (75%) and participating in e-learning (75%). 60% of parents agree that prolonged screen time is harmful to children's eye health. It was seen that children were spending >4 hrs/day using electronic devices which is 48% since the pandemic began, up from 20% before the pandemic with a *P* value of <0.05. Overall, 75% of parents believed myopia to be a very/somewhat serious problem for their children. 61% of parents correctly answered that glasses are not the only option for myopia. **Conclusion:** Parents, as well as children, had increased screen time as compared to the pre-pandemic situation in activities like watching TV, and using a smartphone which included playing online games and e-learning. Children's screen time had doubled compared to pre-pandemic in almost all age groups. Parents should further be educated on how to control their children's screen time. Parents had adequate knowledge about myopia and risk factors but further awareness about it is required.

Keywords: COVID19, myopia, screen time

INTRODUCTION

The COVID-19 pandemic has transformed family life in many ways.[1] The lockdown following COVID-19 has changed the way a large proportion of people around the world go about their lives.[2] Around the world, several schools and many workplaces were closed or partially closed resulting in transitioning of activities that once took place outside of the home, to virtual implementation in the home environment.[3] This has resulted in higher use of digital media such as desktops, laptops, tablets, computers, and mobile devices.[4] Viewing or using anything with a screen, including a computer, television (TV), video games, and digital versatile disc, is defined as screen time (ST).[5] Parents are in the best position to help their children by interacting with them and providing knowledge about screen use to distract them from uncontrolled ST during this pandemic.[6]

According to the data provided by UNESCO (2020), by April 2nd, about 1.5 billion (84.8%) of students (considering all school levels) were affected by this pandemic which led to important challenges to the student learning process.[7] For children, this transition meant adapting to digital or e-learning approaches in the absence of face-to-face, classroom-based learning, friends, and a

Aksha Shetty, Nehal Naik, Ugam P. S. Usgaonkar

Department of Ophthalmology, Goa Medical College, Bambolim, Goa, India

Address for correspondence: Ms. Aksha Shetty, Department of Ophthalmology, Goa Medical College, Bambolim - 403 201, Goa, India.
E-mail: akshashetty70@gmail.com

Submitted: 29-Sep-2022 **Revised:** 03-Dec-2022
Accepted: 05-Dec-2022 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	Quick Response Code
DOI: 10.4103/kjo.kjo_108_22	

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Shetty A, Naik N, Usgaonkar UP. Parents' perception about children screen time and myopia during covid-19 pandemic. Kerala J Ophthalmol 2023;35:161-7.

supportive school environment.[3] In a bid to adjust to this new way of life, governments all over the world providing different solutions to reach out and engage with the students. For all educational levels, the digital mode to deliver learning content, requiring computer, and internet access was the most used, followed by broadcast responses using television, and then radio.[7] Furthermore, the process of studying now includes video conferences and online discussions, and assignments are sent online as well.[8]

Myopia is a major global public health and economic problem with an estimated 1.95 billion people worldwide having myopia.[9] With the rise of virtual learning and more time indoors due to COVID-19 safety measures, the worry of myopia in children has increased. The etiology of myopia is multifactorial, involving the interplay between genetic, environmental and behavioral factors, with increased digital screen time, limited outdoor activities, intensive education, age of myopia onset, and time spent reading continuously or in long periods of close work.[10,11] Several studies have identified that computer usage, watching or reading on a computer and smartphone screen at close distances can increase the risk factor for the development or progression of myopia, especially in younger age groups.[2,12] Chances are that most children have already developed a habit of prolonged ST and many parents might also be spending more time using digital devices or doesn't restrict their children's ST during this COVID-19 pandemic.[13]

A study in China also reported that children had a lower risk of developing myopia if their parents paid attention to their vision from a young age, highlighting the indispensable role that parents play in myopia management.[14] The onset of myopia has also shifted to a younger age which is a concern, as younger children exhibit more rapid myopia progression and are more likely to reach higher levels of myopia. This can substantially increase the risk of developing sight-threatening conditions including retinal detachment, myopic maculopathy, glaucoma, cataracts, and other ocular disorders.[15,16]

While school closures may be short-lived, increased digital ST, near work, and limited outdoor activities could have a long-term negative impact on the onset and progression of myopia.[13,17]

Thus, the present study aims to answer the following questions: Do children spend too much time in screen-related activities? How concerned are parents about children's ST? What is the parents' perception regarding the effects of uncontrolled ST on children?[18] and the impact of increased digital device usage during the COVID-19 pandemic on myopia.

METHODOLOGY

A cross-sectional-based study was conducted from June to November 2021 among the Goan population. Subjects with a child between the age of 3 and 18 years and guardians that were residing with these children for at least the past 3 years were included in the study. Subjects with at least one child between the age of 3 and 18 years were included, and with more than one child response for the oldest child within the age group was considered. The questionnaire framework used to develop the e-survey for parents was as reported by the Ipsos poll conducted between May 29 and June 2, 2020, on behalf of The Global Myopia Awareness Coalition (GMAC).[19] This gave a guide to the structure of sample questions for parents that were used in this online survey. Based on the responses from the pilot samples, the questionnaire was accordingly modified. A total of four hundred and thirteen subjects participated in the study.

The e-survey used to collect participants' responses was designed on Google forms. All participants were immediately directed to an online page comprising three parts: The first part covered the demographic information including Name, Age of the parent and child, Occupation and Level of education. The second part consisted of 35 questions related to parent perception of screen time and comparison regarding the use of digital devices by parents and children before and since the COVID-19 outbreak. The third part studied the parent attitude toward myopia. The study was distributed on social media platforms (WhatsApp, Telegram, Facebook, Instagram) among targeted individuals and was encouraged to forward the link to our survey.

Only fully completed responses were included. Repeated submissions from the same participants were prohibited by linking each response with their IP address on the Google forms web page. The online questionnaire along with the objective and a short idea about the study was sent to the participants and formal online consent was obtained. Participation was entirely voluntary and their privacy was considered during data collection and analysis.

Parents' perceptions about screen-based activities like watching TV, playing games, e-learning, etc., were assessed by six responses: Much more time, A little more time, About the same time, A little less time, Much less time, and Not applicable. The time spent using electronic devices and playing video games was measured by the following responses: <1 hour, 1-2 hours, 3-4 hours, 4-5 hours, 6+ hours, and not applicable/Don't know. The data were collected from Google forms, tabulated using Microsoft Excel and analyzed

in SPSS software. Gender and age differences in parent perception-related questions as well as parents and children's screen time per day using electronic devices and playing video/online games were explored using the paired t test.

Ethical Committee

The study was approved by institutional ethics committee in June 2021 and adhered to the tents of the declaration of Helsinki.

RESULTS

Parents of four hundred and thirteen children (226 boys and 187 girls) were enrolled in the study with a mean age of 39.75 ± 8.35 years, out of which 55.9% (n = 213) were mothers. Table 1 demonstrates demographic data. Fifty-six children who participated in the study were myopic according to parental responses. 18 myopes were from the 11- to 13-year-old age group. There was a significant relationship between the age of the parent and children's myopia (p-value <0.05) whereas there was no significant relation seen between gender and knowledge about myopia.

The majority of the parents felt that their child is spending more time using smartphones (79%), television (73%), and video games (51%). The data also reveal a smaller number of children were using VR headsets (11%), cameras/camcorders (15%), and radio (13%) with parents indicating these devices were not applicable. Figure 1 shows Most of the parents say their child is spending more time playing video/online games (75%), participating in remote or e-learning (75%), watching online movies/shows (66%), and texting/messaging (51%). Also, parents of children between 14 and 17 years felt the same about video chatting (55%) and social media (69%).

Most of the parents (72%) expect their family's screen time to decrease after COVID-19 restrictions are lifted with 55% of parents comfortable with their children's screen time. 60% of parents agree that prolonged screen time is harmful to children's eye health, with 69% agreeing that video gaming is harmful, while 71% of parents are trying to find outdoor activities to do with their children. Only 41% of parents are looking for ways to help limit their child's screen time. Half of the parents (52%) felt that they are spending a long period viewing a screen without stopping and it was even higher for their children (67%). 58% of parents also agree that it is difficult to find activities for their children that do not use screens. 43% of parents say that their child in the last three months has expressed discomfort in his or her eyes after viewing a screen for an extended period which before the coronavirus outbreak began was at 31% as shown in Table 2.

Table 3 shows many parents say that they are spending >4 hrs/day using electronic devices which is 39% since the pandemic began, up from 30% before the pandemic. This hike is even more in parents with children 3–6yrs of age (49%, from 31%). There was a significant difference with a *P* value of <0.05.

Children's screen time doubled since the COVID-19 pandemic began as it was seen that children were spending >4 hrs/day

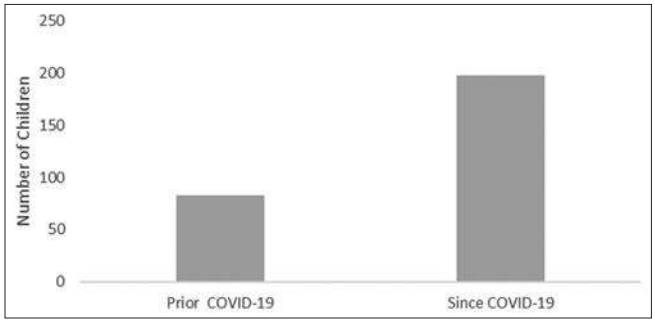


Figure 1: Average time per day child spent using electronic devices and playing video/online games (More than Four Hours Summary)

Table 1: Tthe demographic distribution of the parents

	Total (*n*=413)	Child 3-6 (*n*=89)	Child 7-10 (*n*=97)	Child 11-13 (*n*=117)	Child 14-17 (*n*=110)
Age (Years)	39.748±8.543	39.747±8.545	39.81±8.538	39.761±8.571	39.799±8.55
Gender					
Male	190 (46.004%)	50 (56.180%)	40 (41.237%)	60 (51.282%)	70 (63.636%)
Female	223 (53.995%)	39 (43.820%)	57 (58.762%)	57 (48.717%)	40 (36.363%)
Relationship with child					
Father	176 (42.615%)	49 (55.056%)	32 (32.989%)	58 (49.572%)	37 (33.636%)
Mother	200 (48.426%)	31 (34.831%)	54 (55.670%)	49 (41.880%)	66 (60%)
Guardian	37 (8.958%)	9 (10.112%)	11 (11.340%)	10 (8.547%)	7 (6.363%)
Qualification					
≥12 Std	194 (46.973%)	27 (30.337%)	42 (43.298%)	60 (51.282%)	65 (59.090%)
Graduate	182 (44.067%)	52 (58.429%)	43 (44.329%)	51 (43.589%)	36 (32.728%)
Post-Graduate and above	36 (8.716%)	9 (10.113%)	12 (12.37%)	6 (5.128%)	9 (8.18%)

Table 2: The total agree summary of parent's perception about following statements

	Total (*n*=413)	Child 3-6 (*n*=89)	Child 7-10 (*n*=97)	Child 11-13 (*n*=117)	Child 14-17 (*n*=110)
I have been trying to find outdoor activities to do with my child	71%	79%	70%	69%	70%
I expect my family's screen time to decrease after COVID-19 restrictions are lifted	72%	64%	77%	78%	70%
Prolonged screen time is harmful to my child (ren)'s eye health	60%	55%	67%	63%	53%
I am actively looking for ways to help limit my child's screen time	41%	50%	51%	31%	35%
My family has gotten creative with activities to do throughout the day	44%	55%	40%	40%	41%
I am spending longer periods of time viewing a screen without stopping	52%	50%	71%	40%	49%
My child is spending a long period of time viewing a screen without stopping	67%	47%	85%	62%	75%
Video gaming is harmful to my child's eye health	69%	74%	69%	66%	67%
It's hard to find activities for my child that do not use screens	58%	60%	55%	57%	61%
I'm comfortable with the amount of time my child spends on an electronic device viewing a screen	55%	65%	54%	52%	49%
As a family, we have been bonding over playing video games	24%	34%	27%	21%	15%
In the last three months since the coronavirus outbreak began, my child has expressed discomfort in his/her eyes after viewing a screen for extended periods of time	43%	33%	39%	49%	50%
Before the coronavirus (COVID-19) outbreak, my child expressed discomfort in his/her eyes after viewing a screen for extended periods of time	31%	18%	24%	45%	41%

Table 3: Average time per day parents spent using electronic devices and playing video/online games (More than Four Hours Summary)

	Time spent on electronic devices					Time spent playing video/online games				
	Total (*n*=413)	Child 3-6 (*n*=89)	Child 7-10 (*n*=97)	Child 11-13 (*n*=117)	Child 14-17 (*n*=110)	Total (*n*=413)	Child 3-6 (*n*=89)	Child 7-10 (*n*=97)	Child 11-13 (*n*=117)	Child 14-17 (*n*=110)
Prior to the COVID-19 outbreak	30%	31%	34%	24%	31%	2%	2%	2%	1%	2%
Since the COVID-19 outbreak	39%	49%	39%	30%	38%	5%	7%	5%	7%	2%

Table 4: Average time per day child spent using electronic devices and playing video/online games (More than Four Hours Summary)

	Time spent on electronic devices					Time spent playing video/online games				
	Total (*n*=413)	Child 3-6 (*n*=89)	Child 7-10 (*n*=97)	Child 11-13 (*n*=117)	Child 14-17 (*n*=110)	Total (*n*=413)	Child 3-6 (*n*=89)	Child 7-10 (*n*=97)	Child 11-13 (*n*=117)	Child 14-17 (*n*=110)
Prior to the COVID-19 outbreak	20%	16%	14%	25%	26%	11%	9%	13%	10%	12%
Since the COVID-19 outbreak	48%	29%	39%	54%	69%	29%	18%	27%	32%	39%

Table 5: Statements about myopia, true or false? Correct Answer Summary

Correct Answers	Total (*n*=413)	Child 3-6 (*n*=89)	Child 7-10 (*n*=97)	Child 11-13 (*n*=117)	Child 14-17 (*n*=110)
Myopia is a hereditary condition-True	43%	34%	47%	53%	39%
There is no way to slow down myopia-False	41%	36%	43%	44%	40%
Myopia can lead to other eye diseases-True	60%	62%	63%	60%	54%
Glasses are the only solution to myopia-False	61%	66%	56%	60%	61%
Myopia occurs due to environmental factors-True	44%	36%	45%	51%	44%

using electronic devices which are 48% since the pandemic began, up from 20% before the pandemic or playing video games (29%, from 11%) with a *P* value of <0.05 as shown in Table 4.

As shown in Table 5, when asked about myopia as a true/false statement, on average about 50% of parents were able to answer correctly, with 61% of parents correctly understanding that glasses are not the only option for myopia and 60% saying that myopia can lead to other eye diseases.

The data in Table 6 show that about half of the parents (48%) believe that watching too much TV can cause myopia. This is followed by too much time staring at a small screen (41%) and hereditary factors (35%).

Half of the parents (51%) felt that childhood-onset myopia is more common than it used to be. Only 34% of parents (whose child is myopic) are concerned that their child's screen time will either worsen their myopia. Overall, 75% of parents

Table 6: Parents knowledge about largest factors that contribute to myopia

Factors	Total (*n*=413)	Child 3-6 (*n*=89)	Child 7-10 (*n*=97)	Child 11-13 (*n*=117)	Child 14-17 (*n*=110)
Hereditary factors	35%	30%	34%	29%	46%
Too much time staring at small screens (phones, tablets, etc.)	41%	39%	42%	34%	49%
Watching too much TV	48%	48%	55%	41%	50%
Video games	15%	13%	21%	17%	10%
Age	16%	19%	13%	20%	11%
Nutrition deficiency	10%	6%	13%	10%	9%
Reading books too closely	10%	9%	11%	16%	5%
Environmental factors	11%	14%	9%	12%	8%
Lack of time outside	18%	20%	28%	12%	14%
Gender	3%	3%	6%	4%	1%
Race	1%	0%	1%	0%	2%
Others	1%	2%	0%	1%	1%
None of the above	5%	4%	3%	7%	5%

believe myopia to be a very or somewhat serious problem for their child.

DISCUSSION

The present study investigates the parent's perception of children's screen time and identifies the perceived factors for increased screen time and myopia during the COVID-19 pandemic. For many parents, it may be difficult to control their children's screen time, while struggling to balance their personal life, working life, and parenting responsibilities during the pandemic. A study was required to understand the parental perception of child's screen time, especially during this pandemic where screen times for both adults and children have increased significantly.

Schools have shifted to online classes to avoid the prolonged disruption in studies of students and this has increased the amount of time looking at a digital screen. Although in most cases this extra ST might be needed for educational purposes, social interaction, distraction, and entertainment. There is a wealth of advice available about how much screen time is too much for children and what types of screen time are detrimental but most of this advice is not meant for the pandemic situation. In this study, many parents felt that their children are spending more time playing video/online games (75%), and watching online movies (66%). Similar findings about TV watching were reported by Daniela Brindova *et al.*[20] 86% of parents agree that teens spend too much time gaming as reported by Michigan Medicine- University of Michigan. Even before COVID-19, there was an increase in the amount of screen use by children.[13] The coronavirus pandemic is changing the way children learn as it was seen that 75% of the children were participating in remote or e-learning and this could affect their eyes.

Significantly, more parents stated that their children are spending >4 hours/day using electronic devices which were 44% since the pandemic compared to 21% before the pandemic began. A similar increase was seen in playing video games (28%, from 13%). AO Eyimaya and Irmak[6] reported that 71.7% of the parents reported that their children's ST had increased reaching approximately 6.42 h/day.

In our study, it was seen that 71% of the parents were trying to find outdoor activities to do with their children and 41% had gotten creative with activities to do throughout the day since the pandemic. Hence in line with screen time rules, creative and physical activities outside the screen use should be included in the daily schedule of the children as this can help in reducing screen time.[21] It was also seen that parents' screen time had increased significantly as 39% of them were spending >4 hrs/day using electronic devices since the pandemic began.

Parents' views of the dominant risk factors for myopia were watching too much TV (48%) followed by too much time staring at a small screen (41%). More than half of the parents (54%) felt that childhood-onset myopia has become more common than it used to be. The continuous and sudden reliance on technology at home, work, in schools, in our cars, and almost every aspect of our lives during this COVID-19 pandemic may be a factor in the increase in the rise of myopia, especially among children who are becoming myopic at a younger age. Increased use of electronic devices competes with activities such as time outdoors, thereby potentially exerting both a direct and indirect influence on myopia development and progression.[22-24] As parents have a great influence on their child's lifestyle choices, there should be public education to aware parents and guardians of myopia and its risk factors.

Older children (14–17yrs) in our study spent more time using electronic devices than younger children (3–13 yrs) as older children are more likely to have a phone which leads to more screen time and near work. McCrann *et al.*[22] reported that the closer working distance of a mobile phone compared to a computer screen or a book places greater visual demands on the ocular system which is important given that it has been identified as a risk factor for myopia.

The parents should discuss with their children appropriate screen time on an individualized basis. Co-viewing or co-sharing of digital content helps in building the parent–child bond and provides an opportunity to keep a look at the digital or media use habits of their children.[2] Even though the majority of parents (72%) in our study reported that they expect their family's screen time to decrease after COVID-19 restrictions are lifted, a great number of children spent over >4 hrs per day on average at a screen. The World Health Organization (WHO) recommends that children up to one year should not spend any time on digital screens, including watching videos or playing games. For children aged 2–4 years, sedentary screen time should be no more than one hour a day, and even less is better. There are no screen-time cut-offs specifically recommended for older children or adolescents by either the WHO or any other government/country health guidelines.[2] 42% of the people were concerned that their child will develop myopia. Only 14% of parents say their child has myopia, but 75% were familiar with it and think it is a serious problem for their child. Although in our study myopic children were relatively small in number (n = 56), they spent significantly more time indoors using electronic devices compared to non-myopes. This supports the observation of J Wang *et al.*[15] and Ip *et al.*[25] that increased amounts of close work contribute to a higher prevalence and severity of myopia. About 50% of the parents are correct in answering a series of true/false statements about myopia. This shows that more knowledge about myopia is necessary among parents.

In response to the increased use of digital screens, the Ministry of Human Resource Development, Government of India, has launched guidelines for digital education ("PRAGYATA"), which recommends states limit daily screen time for online lectures or teaching to one session of 30 min for pre-primary (0.5 h), two sessions of up to 45 min each for 1st to 8th standard (1.5 h), and four sessions of 30–45 min duration for 9th to 12th standard (3 h).[2]

CONCLUSION

Stay-at-home orders during the COVID-19 pandemic presented unique challenges for parents and children. COVID-19 has changed the way and amount of time we use digital devices. Many parents are relaxing screen time rules for TV and video games to keep children occupied while social distancing. This has doubled the screen time in parents as well as children as compared to the pre-pandemic situation. Prolonged use of screen devices is becoming the new norm in the modern lifestyle.

Most children were involved in increased digital activities like watching TV and using a smartphone which included playing online games and e-learning. Many parents were trying to find outdoor activities and be creative to limit their child screen time. Parents had somewhat adequate knowledge about myopia. Teachers, pediatricians, and social and community health workers can further increase awareness among parents regarding screen time and myopia. It is necessary to revise the existing recommendation on screen time for children. Using screens to communicate with family and friends should be identified separately from using digital devices for learning purposes. The critical role parents will play in addressing and understanding their level of awareness of myopia risks and of potential adverse impacts of screen time on children and its relation to myopia is going to help them during this pandemic.

The results of this study must be regarded from the perspective of the following limitations participants self-reported the time spent by their children in daily activities. Also, the parents could report higher or lower time to all tasks relative to children. The accuracy of this approach is difficult to gauge.

The attitudes of others such as children themselves, teachers, and clinicians were not explored herein, but are also important.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Hammons AJ, Villegas E, Robart R. It's been negative for us just all the way across the board: Focus group study exploring parent perceptions of

child screen time during the COVID-19 pandemic. JMIR Pediatr Parent 2021;4:e29411.
2. Singh S, Balhara YPS. "Screen-time" for children and adolescents in COVID-19 times: Need to have the contextually informed perspective. Indian J Psychiatry 2021;63:192-5.
3. Eyler AA, Schmidt L, Beck A, Gilbert A, Kepper M, Mazzucca S. Children's physical activity and screen time during COVID-19 pandemic: A qualitative exploration of parent perceptions. Health Behav Policy Rev 2021;8:236-46.
4. Sultana A, Tasnim S, Hossain MM, Bhattacharya S, Purohit N. Digital screen time during the COVID-19 pandemic: A public health concern. F1000Research 2021;10:81.
5. Usgaonkar U, Shet Parkar SR, Shetty A. Impact of the use of digital devices on eyes during the lockdown period of COVID-19 pandemic. Indian J Ophthalmol 2021;69:1901-6.
6. Eyimaya AO, Irmak AY. Relationship between parenting practices and children's screen time during the COVID-19 Pandemic in Turkey. J Pediatr Nurs 2021;56:24-9.
7. Cunha J, Silva C, Guimarães A, Sousa P, Vieira C, Lopes D, *et al*. No children should be left behind during COVID-19 pandemic: Description, potential reach, and participants' perspectives of a project through radio and letters to promote self-regulatory competences in elementary school. Front Psychol 2021;12:647708.
8. Susilowati IH, Nugraha S, Alimoeso S, Hasiholan BP. Screen time for preschool children: Learning from home during the COVID-19 pandemic. Glob Pediatric Health 2021;8:2333794X211017836.
9. Sheppard AL, Wolffsohn JS. Digital eye strain: prevalence, measurement and amelioration. BMJ Open Ophthalmol 2018;3:e000146.
10. Yang GY, Huang LH, Schmid KL, Li CG, Chen JY, He GH, *et al*. Associations between screen exposure in early life and myopia amongst Chinese preschoolers. Int J Environ Res Public Health 2020;17:1056.
11. Rodríguez-Rey R, Garrido-Hernansaiz H, Collado S. Psychological impact and associated factors during the initial stage of the coronavirus (COVID-19) pandemic among the general population in Spain. Front Psychol 2020;11:1540.
12. Sung YT, Chang KE, Liu TC. The effects of integrating mobile devices with teaching and learning on students' learning performance: A meta-analysis and research synthesis. Compu Educ 2016;94:252-75.
13. Wong CW, Tsai A, Jonas JB, Ohno-Matsui K, Chen J, Ang M, *et al*. Digital screen time during the COVID-19 pandemic: Risk for a further myopia boom?. Am J Ophthalmol 2021;223:333-7.
14. Salim AT, Keel S, Foreman J, Dirani M. Awareness of myopia: A survey among parents residing in Singapore, 2019, PREPRINT (Version 5) available at Research Square. [https://doi.org/10.21203/rs.2.10314/v5] [Last accessed on 2022 Jul 20].
15. Wang J, Li Y, Musch DC, Wei N, Qi X, Ding G, *et al*. Progression of myopiainschool-agedchildrenafterCOVID-19homeconfinement. JAMA Ophthalmol 2021;139:293-300.
16. Holden B, Sankaridurg P, Smith E, Aller T, Jong M, He M. Myopia, an underrated global challenge to vision: Where the current data takes us on myopia control. Eye (Lond) 2014;28:142-6.
17. Dunton GF, Do B, Wang SD. Early effects of the COVID-19 pandemic on physical activity and sedentary behavior in children living in the US. BMC Public Health 2020;20:1351.
18. Hinkley T, McCann JR. Mothers' and father's perceptions of the risks and benefits of screen time and physical activity during early childhood: A qualitative study. BMC Public Health 2018;18:1271.
19. Brindova D, Pavelka J, Ševčikova A, Žežula I, van Dijk JP, Reijneveld SA, *et al*. How parents can affect excessive spending of time on screen-based activities. BMC public health 2014;14:1-8.
20. Brindova D, Pavelka J, Ševčikova A, Žežula I, van Dijk JP, Reijneveld SA, *et al*. How parents can affect excessive spending of time on screen-based activities. BMC Public Health 2014;14:1261.
21. Schmidt SC, Anedda B, Burchartz A, Eichsteller A, Kolb S, Nigg C, *et al*. Physical activity and screen time of children and adolescents before and during the COVID-19 lockdown in Germany: A natural experiment. Sci Rep 2020;10:21780.
22. McCrann S, Flitcroft I, Lalor K, Butler J, Bush A, Loughman J. Parental attitudes to myopia: A key agent of change for myopia control?. Ophthalmic Physiol Opt 2018;38:298-308.
23. French AN, Ashby RS, Morgan IG, Rose KA. Time outdoors and the prevention of myopia. Exp Eye Res 2013;114:58-68.
24. Wu PC, Huang HM, Yu HJ, Fang PC, Chen CT. Epidemiology of myopia. Asia-Pacific J Ophthalmol (Phila) 2016;5:386-93.
25. Ip JM, Saw SM, Rose KA, Morgan IG, Kifley A, Wang JJ, *et al*. Role of near work in myopia: Findings in a sample of Australian school children. Invest Ophthalmol Vis Sci 2008;49:2903-10.

Original Article

A cross-sectional study to determine the relationship between diabetic retinopathy and diabetic nephropathy in type 2 diabetes mellitus patients in South India

ABSTRACT

Background: This cross-sectional study aims to determine the risk factors and correlation between diabetic retinopathy (DR) and diabetic nephropathy (DN) in type 2 diabetes mellitus in South India. **Materials and Methods:** A hospital-based analytical cross-sectional study was conducted on 200 type 2 diabetes mellitus patients and were assessed for diabetic retinopathy and nephropathy. Patients were classified into two groups: no-diabetic nephropathy (Group A) and diabetic nephropathy (Group B) based on eGFR. Fundoscopy was performed in all patients to look for DR. Multivariate regression analysis was used to determine risk factors associated with diabetic nephropathy. This study was approved by the institutional review board, and written informed consent was obtained from all participants. **Statistical Analysis:** Statistical Package for Social Sciences (SPSS) version 20.0 for Windows was used. Descriptive statistical methods were used to outline the basic characteristics, and a *P* value less than 0.05 was considered statistically significant. Differences between the groups were analyzed using independent-sample t-test for continuous variables and χ^2 test for categorical variables. **Results:** In this study, 52% patients with DN had retinopathy when compared to 23% patients in no-DN ($P < 0.001$). The distribution of different types of retinopathies was 44% NPDR, 28% PDR, and 32% CSME in patients with DN and 31% NPDR, 8% PDR, and 7% CSME in the no-DN group ($P < 0.001$). The age, hypertension, duration of diabetes, serum creatinine, urine protein levels, and diabetic retinopathy gradings were found to be more positively correlated with DN; no diabetic retinopathy and insulin treatment data showed negative correlation. Multivariate regression analysis confirmed age, creatinine, eGFR, DR, and CSME as risk factors for progression to DN ($P < 0.05$). **Conclusion:** The results of our study suggest that diabetic nephropathy has a positive correlation with diabetic retinopathy in type 2 diabetes mellitus patients. We found that PDR and CSME were associated with diabetic nephropathy, and PDR and CSME were risk factors for DN. Hence, renal parameters can be used as a reliable predictor for diabetic retinopathy in type 2 diabetes mellitus patients and also contribute to prevention of DR.

Keywords: Diabetic nephropathy, diabetic retinopathy, type 2 diabetes mellitus

INTRODUCTION

Diabetes mellitus is rising at an alarming rate in every part of the country; its control and proper care of patients is very necessary. Uncontrolled diabetes can lead to microvascular complications like diabetic nephropathy, neuropathy, and retinopathy; nephropathy and retinopathy being the most common among them.[1] As they progress to end-stage renal disease (ESRD) and blindness, they impose enormous medical, economic, and social costs on both the patient and the healthcare system. India had 40.9 million diabetic patients in the year 2007, and the number is expected to increase up to 79.4 million by 2030.[2]

Diabetic nephropathy results from long-standing diabetes mellitus.[3] It affects the minute blood vessels in glomerulus which is critical for blood filtration. Essential features of this co-morbidity are excessive protein in urine (microalbuminuria to macroalbuminuria), high

Anjali L. Roche, Rajashree S. Prabhu, Indu Govind

Department of Ophthalmology, East Point Hospital, Bengaluru, Karnataka, India

Address for correspondence: Dr. Anjali L. Roche, Department of Ophthalmology, East Point Hospital, Bengaluru, Karnataka, India.
E-mail: anjali.litaroche@eastpoint.ac.in

Submitted: 12-May-2022 **Revised:** 15-Oct-2022
Accepted: 06-Nov-2022 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	Quick Response Code
DOI: 10.4103/kjo.kjo_69_22	

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Roche AL, Prabhu RS, Govind I. A cross-sectional study to determine the relationship between diabetic retinopathy and diabetic nephropathy in type 2 diabetes mellitus patients in South India. Kerala J Ophthalmol 2023;35:168-73.

blood pressure, and most importantly progressive kidney impairment.

Diabetic retinopathy is a microangiopathy in which small blood vessels are particularly vulnerable to damage from high glucose levels. It is one of the major reasons for blindness in the normal population.[4] As the disease progresses, it can cause growth of new vessels in the clear vitreous humor which can further bleed and cause blurring of vision secondary to diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR).

This research aims to determine the risk factors and correlation between diabetic retinopathy and diabetic nephropathy in type 2 diabetes mellitus individuals for early detection and treatment for better visual prognosis.

MATERIALS AND METHODS

A hospital-based analytical cross-sectional study was conducted on type 2 diabetes mellitus patients and was assessed for diabetic retinopathy and nephropathy. The study population included 200 diabetic patients with/without diabetic retinopathy and diabetic nephropathy, and informed consent was obtained from all patients. Patients with (1) type 1 diabetes mellitus and (2) diagnosed with retinopathy or nephropathy due to causes other than diabetes mellitus were excluded from the study.

A written informed consent was obtained from the study participants, and Institutional Ethical Committee approval was obtained for this study. A detailed medical history, duration of diabetes, treatment history, and history of comorbidities such as hypertension, ischemic heart disease, diabetic foot, and dyslipidemia were asked. Multiple baseline biochemical tests were performed with the patients' consent for FBS, PPBS, glycated hemoglobin (HbA1c), and renal profile (blood urea, serum creatinine, urine protein, microalbumin, eGFR).

A dilated fundus examination was done using direct, indirect ophthalmoscope and slit-lamp biomicroscopy. The staging of diabetic retinopathy was determined by comparison with standard photographs from the Early Treatment Diabetic Retinopathy Study (ETDRS)[5] and scored according to Airlie House Classification system.[6,7]

- Level 10 - No apparent retinopathy
- Level 35 - Mild non-proliferative diabetic retinopathy—microaneurysms only
- Level 43-47 - Moderate non-proliferative diabetic retinopathy—more than just microaneurysm (s) but less than severe non-proliferative diabetic retinopathy.
- Level 53 - Severe non-proliferative diabetic retinopathy—Any of the following: >20 intra-retinal hemorrhages in each of four quadrants, definite venous beading in ≥2 quadrants, prominent intra-retinal microvascular abnormalities in ≥1 quadrant, or no signs of proliferative retinopathy.
- Level 61 - Proliferative diabetic retinopathy—one or more of the following: neovascularization and/or vitreous or preretinal hemorrhages.
- Diabetic macular edema –
  - No macular edema – No exudates and no apparent thickening within 1 disc diameter from fovea.
  - Exudates or apparent thickening within 1 disk diameter from fovea.[8]

The criteria for diagnosing type 2 DM given by WHO and ADA are as follows.[9]

- FBS ≥126 mg/dl (fasting = no caloric intake for at least 8 hours).
- PPBS ≥200 mg/dl.

Hypertension was diagnosed by a history of hypertension/drug therapy, or blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg was recorded on three consecutive occasions.[10]

Diabetic nephropathy was defined as (1) eGFR less than 60 mL/min/1.73m^2 and/or (2) albuminuria 30 µg/mg or above.[11] Renal failure is defined as eGFR <30 mL/min/1.73m^2. The Chronic Kidney Disease-Epidemiology Collaboration formula was used for calculation of eGFR.[12] Microalbuminuria is defined as excretion of 30–300 mg of albumin per 24 hours on two of three urine collections. The detection of low levels of albumin excretion (microalbuminuria) has been linked to the identification of incipient diabetic kidney disease.

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 20.0 for Windows was used. Data were expressed as means ± SD. Descriptive statistical methods were used to outline the basic characteristics, and a P value less than 0.05 (two-tailed) was considered statistically significant. Differences between the groups were analyzed using independent-sample t-test for continuous variables and χ^2 test for categorical variables. Pearson's correlation coefficient (r) was also used to examine the association of clinical characteristics with DN. Binary logistic regression analysis was performed using no-DN and DN as dependent variable to identify the risk factors associated with diabetic nephropathy. Risk factors that were identified as affecting DN by univariate analysis ($P < 0.1$) were included in the multivariate analysis to determine the factors most associated with DN. The association between each risk

factor and diabetic nephropathy was determined by odds ratio, along with its 95% confidence interval (95%CI).

OBSERVATION AND RESULTS

Out of total of 200 subjects with type 2 diabetes mellitus, 100 patients were found to have DN and remaining 100 patients had no-DN, and a male predominance of 54% was seen. Table 1 provides the comparison of characteristics between the no-DN group with DN group. The mean age of patients with no-DN vs. DN was 54.05 ± 9.73 vs. 62.66 ± 11.15 years, $P < 0.001$.

Patients with DN were more likely to have hypertension (56% in DN vs. 27% in no-DN group, $P < 0.001$) and higher systolic blood pressure (129 ± 13.45 mmHg vs. 124.10 ± 10.83 mmHg, $P = 0.005$) [Figure 1].

Patients with DN had a longer duration of DM (10.87 ± 7.84 vs. 6.96 ± 5.67 years, $P < 0.001$) [Figure 2], higher serum creatinine levels (1.54 ± 0.83 vs. 0.70 ± 0.15 mg/dL, $P < 0.001$), higher urine protein levels (64.15 ± 124.57 vs. 12.67 ± 43.36 mg/dL, $P < 0.001$), and a lower eGFR level (53.02 ± 22.49 vs. 102.71 ± 10.34 mL/min/1.73m^2, $P < 0.001$) [Figure 3]. Over 42% of patients with DN were on insulin as compared to 19% of those in no-DN group ($P < 0.001$).

Table 1: Comparison of characteristics between the no-DN group with DN group

	No-DN, *n*=100	DN, *n*=100	*P*	*r*
Age, y	54.05 (9.73)	62.66 (11.15)	<0.001	0.358
HTN, %	27	56	<0.001	0.294
SBP, mmHg	124.10 (10.83)	129 (13.45)	0.005	0.198
DBP, mmHg	83.50 (8.91)	87.30 (10.71)	0.007	0.190
Duration of DM, y	6.96 (5.67)	10.87 (7.84)	<0.001	0.276
FBG, mg/dL	188.72 (82.05)	192.41 (96.05)	0.771	0.021
HbA1c, %	8.66 (2.50)	8.66 (2.28)	0.994	0.001
Creatinine, mg/dL	0.70 (0.15)	1.54 (0.83)	<0.001	0.576
eGFR, mL/min/1.73m^2	102.71 (10.34)	53.02 (22.49)	<0.001	0.819
Urine protein, mg/dL	12.67 (43.36)	64.15 (124.57)	<0.001	0.267
On OHAs alone, %	95	84	0.11	0.179
On insulin alone, %	19	42	<0.001	-0.250
No DR, %	60	22	<0.001	-0.386
NPDR, %	31	44	<0.001	0.260
PDR, %	8	28		
CSME, %	7	32		

*DN, diabetic nephropathy; *r*, Pearson's correlation coefficient; HTN, hypertension, SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate; OHA, oral hypoglycemic agent; DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; CSME, clinically significant macular edema

The distribution of different types of retinopathies was 44% NPDR, 28% PDR, and 32% CSME in patients with DN and 31% NPDR, 8% PDR, and 7% CSME in the no-DN group ($P < 0.001$) [Figure 4]. The age, hypertension, duration of diabetes, serum creatinine, eGFR, urine protein levels, and diabetic retinopathy gradings were found to be positively correlated with DN; insulin treatment data showed negative correlation.

Table 2 shows the risk factors for diabetic nephropathy determined by logistic regression analysis. Most of the risk factors like age (adjusted OR [aOR] 1.067; 95% CI 1.034 1.100), creatinine (aOR 2.94; 95% CI 1.503–1.856), eGFR (aOR 2.283; 95% CI 1.200–3.450), urine protein (aOR 1.00; 95% CI 0.981 1.010), PDR (aOR 4.147; 95% CI 1.730 9.940), and CSME (aOR 5.862; 95% CI 2.427 14.158) were significantly associated with diabetic nephropathy.

DISCUSSION

The prevalence of overt nephropathy of 2.2% (>850,000 individuals) was seen in a study done in urban South Indian population.[13] The absolute number of subjects with diabetic nephropathy thus presents an economic burden to both the individual and the society. Low awareness in both general public and medical fraternity as well as heavy reliance of alternative medical practices has led to an increased prevalence of diabetic nephropathy and retinopathy in our population compared to more developed regions. This cross-sectional study included 200 patients who were diagnosed with type 2 diabetes mellitus, of which 100 were diagnosed to have DN and 100 no-DN. A male predominance of 54% was seen among the patients. The age factor showed significance in DN individuals.

Huang *et al*.[1] study postulated that genes and gender are known contributing factors to diabetic nephropathy, which can be used for diabetic nephropathy risk assessment.

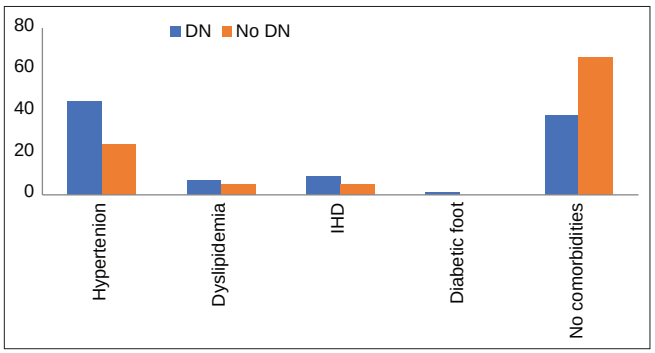


Figure 1: Prevalence of co-morbidities among patients with DN and without DN

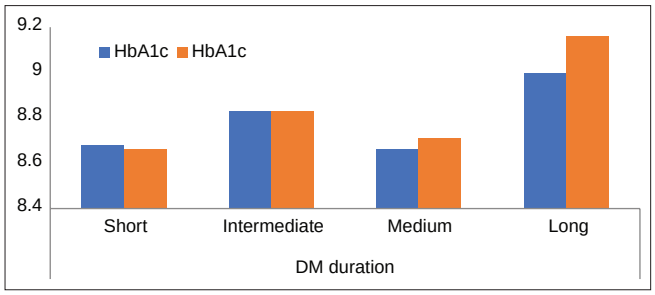


Figure 2: Distribution of HbA1c among patients with DN and without DN

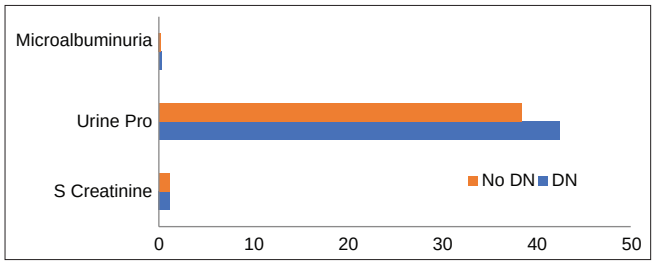


Figure 3: Distribution of biomarkers of renal function among pathients with DN and without DN

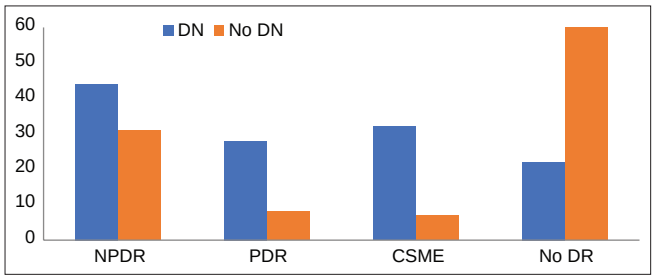


Figure 4: Prevalence of diabetic retinopathy among patients of with DN and without DN

The major risk factors for DR are duration of diabetes and degree of glycemic control, and for every 5-year increase in duration of diabetes, the risk for DR was increased by 1.89-fold, whereas a 2% increase in HbA1c resulted in a 1.7-fold increase in risk for DR.[9] Glycemic variability and dyslipidemia were significantly associated with progression of diabetic nephropathy in T2DM.[14] The mean duration of diabetes among diabetic nephropathy individuals was longer compared to no DN, suggesting the longer the duration of diabetes the higher the prevalence of nephropathy. It was observed that subjects with DN had worse glycemic control than those with no-DN. However, it did not retain significance in the final logistic regression analysis.

In a study conducted by Jawa *et al*.,[15] type 2 diabetes with marked proteinuria and retinopathy most likely have DN, whereas those without retinopathy have a high incidence of non-diabetic glomerular disease. Both eGFR and serum creatinine were found to have a strong association with DN ($P < 0.001$). Also, the presence and severity of diabetic retinopathy are closely associated with markers of diabetic kidney disease, especially lower estimated glomerular filtration.[16]

Song *et al*.[14] found the prevalence of nephropathy among individuals with retinopathy was 35.6%, showing a significant association between nephropathy and development of retinopathy ($P < 0.001$).[14] In this study, 75% patients of DN had DR (mostly PDR and CSME) which was significantly higher than in patients with no DN (32%, $P < 0.002$). This may be secondary to poor glycemic control among DN patients. The distribution of various types of retinopathies among DN was 44% NPDR, 28% PDR, 32% CSME, and 31% NPDR, and 8% PDR and 7% CSME among no-DN. An association between DR (PDR and CSME) and DN was significant in the univariate χ^2 test and multivariate logistic regression analysis which was consistent with some previous studies that have shown prevalence rates of DN to be significantly higher among patients with CSME.[17] Proliferative diabetic retinopathy association with microalbuminuria and DR association with overt nephropathy were seen in Korean DM patients.[18] In the Chennai Urban Rural Epidemiology Study, nephropathy increased the odds for developing DR by 2.4 times.[19] In the Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Study, a twofold higher risk of DR was seen in people with microalbuminuria.[18] Hence, diabetic retinopathy, especially at the proliferative stage, could be a useful tool for diagnosis, screening, and predictor of progression of diabetic nephropathy.[17,20]

Of all the DN patients surveyed, nearly 51% of them were on OHAs and 31% on insulin treatment.

Of the patients with diabetic nephropathy, 78% of them showed normal to early deterioration of the renal function. Here they either had normal or +/- 5 mg/day of protein in the urine. The rest 22% who had stage 1 nephropathy had high proteins in the urine also showed some amount of microalbumin the urine. These two are the basic indicators of renal function deterioration.

Hence, among the patients surveyed and researched, it can be rightly said that those with good control over their sugars had good health, i.e., less chances of any co-morbidities. Others who have poor control of their sugars had high chances of having retinopathy or nephropathy.

In a population-based study among Sudanese adults with diabetes, hypertension was identified as risk factor for both retinopathy and nephropathy.[21] This current study on Indian patients showed a higher prevalence of hypertension 41% in subjects with DN than in those with no-DN, and SBP was positively associated with DN.

Table 2: Risk factors for diabetic nephropathy determined by logistic regression analysis

Variable	Univariate			Multivariate		
	OR	95% CI	*P*	aOR	95% CI	*P*
Age	1.08	1.044-1.108	<0.001	1.067	1.034-1.100	<0.001
HTN, %	3.441	1.903-6.222	<0.001	2.666	1.430-4.971	<0.001
SBP, mmHg	1.034	1.010-1.058	0.006	0.967	0.925-1.012	0.146
DBP, mmHg	1.040	1.010-1.070	0.008	0.950	0.897-1.007	0.082
Duration of DM, y	1.094	1.043-1.147	<0.001	1.070	1.020-1.124	<0.001
FBG, mg/dL	1.00	0.997-1.004	0.769			
HbA1c, %	1.00	0.891-1.124	0.994			
Creatinine, mg/dL	2.50	0.206-0.404	<0.001	2.94	1.503-1.856	0.001
eGFR, mL/min/1.73m^2	2.58	1.387-3.670	<0.001	2.283	1.200 – 3.450	0.001
Urine protein (mg/dL)	1.01	1.003-1.015	0.003	0.996	0.981-1.010	0.562
On OHA's alone, %	3.619	1.271-10.303	0.016			
On insulin alone, %	0.324	0.171-0.613	0.324			
No DR, %	0.188	0.101-0.349	<0.001	0.097	0.040-0.235	<0.001
NPDR, %	1.749	0.980-3.121	0.059	1.473	0.798-2.717	0.027
PDR, %	4.472	1.923-10.402	<0.001	4.147	1.730-9.940	<0.001
CSME, %	6.252	2.605-15.007	<0.001	5.862	2.427-14.158	<0.001

*CI, confidence interval; HTN, hypertension, SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate; OHA, oral hypoglycemic agent; DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; CSME, clinically significant macular edema

The limitations our study had were as follows. Firstly, the sample size is smaller compared to previous similar studies. Secondly, the relationship between DN and DR may vary depending on the treatment regimen for DN. Thirdly, hypertension is not only a risk factor but also a consequence of renal damage. Hence, causality between hypertension and DN is impossible to infer.

CONCLUSION

The results of our study suggest that diabetic nephropathy has a positive correlation with diabetic retinopathy in type 2 diabetes mellitus patients. We found that PDR and CSME were associated with diabetic nephropathy, and PDR and CSME were risk factors for DN. The age, hypertension, duration of diabetes, serum creatinine, urine protein levels, and diabetic retinopathy gradings were found to be positively correlated with DN; fasting blood glucose levels and insulin treatment data showed negative correlation. In our country India, renal parameters like eGFR and/or albuminuria can be used by physicians as markers to refer patients to the ophthalmologist for prompt management of diabetic retinopathy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Huang GM, Huang KY, Lee TY, Weng JT. An interpretable rule-based diagnostic classification of diabetic nephropathy among type 2 diabetes patients. BMC Bioinformatics 2015;16(Suppl 1):S5.
2. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: Global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011;94:311-21.
3. Lim AK. Diabetic nephropathy–complications and treatment. Int J Nephrol Renovasc Dis 2014;7:361-81.
4. Stewart MW. Treatment of diabetic retinopathy: Recent advances and unresolved challenges. World J Diabetes 2016;7:333-41.
5. Early Treatment Diabetic Retinopathy Study Research Group. Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics: ETDRS report number 7. Ophthalmology 1991;98 (5 Suppl):741-56.
6. Diabetic Retinopathy Study Research Group. Diabetic retinopathy study report number 6. Design, methods, and baseline results. Report number 7. A modification of the Airlie House classification of diabetic retinopathy. Prepared by the diabetic retinopathy. Invest Ophthalmol Vis Sci 1981;21:1-226.
7. Wilkinson CP, Ferris FL 3rd, Klein RE, Lee PP, Agardh CD, Davis M, *et al*.; Global Diabetic Retinopathy Project Group. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003;110:1677-82.
8. Stevens PE, Levin A. Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members*. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Annals of internal medicine 2013;158:825-30.

9. Rema M, Premkumar S, Anitha B, Deepa R, Pradeepa R, Mohan V. Prevalence of diabetic retinopathy in urban India: The Chennai Urban Rural Epidemiology Study (CURES) eye study, I. Invest Ophthalmol Vis Sci 2005;46:2328-33.
10. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, *et al*. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension 2003;42:1206-52.
11. Stevens LA, Schmid CH, Greene T, Zhang YL, Beck GJ, Froissart M, *et al*. Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study equations for estimating GFR levels above 60 mL/min/1.73 m2. Am J Kidney Dis 2010;56:486-95.
12. Lee WJ, Sobrin L, Lee MJ, Kang MH, Seong M, Cho H. The relationship between diabetic retinopathy and diabetic nephropathy in a population-based study in Korea (KNHANES V-2, 3). Invest Ophthalmol Vis Sci 2014;55:6547-53.
13. Unnikrishnan R, Rema M, Pradeepa R, Deepa M, Shanthirani CS, Deepa R, *et al*. Prevalence and risk factors of diabetic nephropathy in an urban South Indian population: The Chennai Urban Rural Epidemiology Study (CURES 45). Diabetes Care 2007;30:2019-24.
14. Song KH, Jeong JS, Kim MK, Kwon HS, Baek KH, Ko SH, *et al*. Discordance in risk factors for the progression of diabetic retinopathy and diabetic nephropathy in patients with type 2 diabetes mellitus. J Diabetes Investig 2019;10:745-52.
15. Jawa A, Kcomt J, Fonseca VA. Diabetic nephropathy and retinopathy. Medical Clinics 2004;88:1001-36.
16. Early Treatment Diabetic Retinopathy Study Research Group. Classification of diabetic retinopathy from fluorescein angiograms: ETDRS report number 11. Ophthalmology 1991;98 (5 Suppl):807-22.
17. El-Asrar AM, Al-Rubeaan KA, Al-Amro SA, Moharram OA, Kangave D. Retinopathy as a predictor of other diabetic complications. Int Ophthalmol 2001;24:1-11.
18. Raman R, Rani PK, Rachepalle SR, Gnanamoorthy P, Uthra S, Kumaramanickavel G, *et al*. Prevalence of diabetic retinopathy in India: Sankara Nethralaya diabetic retinopathy epidemiology and molecular genetics study report 2. Ophthalmology 2009;116:311-8.
19. Pradeepa R, Anitha B, Mohan V, Ganesan A, Rema M. Risk factors for diabetic retinopathy in a South Indian type 2 diabetic population—the Chennai Urban Rural Epidemiology Study (CURES) Eye Study 4. Diabetic Medicine 2008;25:536-42.
20. Villar G, Garcia Y, Goicolea I, Vazquez JA. Determinants of development of microalbuminuria in normotensive patients with type 1 and type 2 diabetes. Diabetes Metab 1999;25:246-54.
21. Ahmed MH, Elwali ES, Awadalla H, Almobarak AO. The relationship between diabetic retinopathy and nephropathy in Sudanese adult with diabetes: Population based study. Diabetes Metab Syndr 2017;11(Suppl 1):S333-6.

Original Article

Awareness and attitude regarding eye donation among undergraduate students of an engineering institution and its implication in Tamil Nadu

ABSTRACT

Background: Corneal blindness is estimated to be the second most prevailing cause of blindness in developing nations. Visual rehabilitation by corneal transplantation is the main choice for the restoration of vision in these cases. The corneal transplant success relies on the availability of high-quality donor eyes. At present, there is a gap between the demand and supply of donor corneal tissues in the developing world. Our study aims to assess the awareness and willingness to eye donation among undergraduate students, especially those from a non-medical background. **Methods:** A single-center, cross-sectional study was conducted on engineering undergraduate students studying in a reputed Multi-disciplinary Institution, located in rural Tamil Nadu during the period August 2018 to March 2019 (8 months). Using random sampling, 507 students were selected for the study. A structured questionnaire was administered to all the participants. For statistical analysis, SPSS software, version 22, was used. **Results:** A total of 507 students participated in the study. The mean age of participants was 19 ± 2 years. In the study group, more than half (499) of the students had awareness about "eye donation," but only 62.2% of students were willing to donate eyes. Among the study participants, 74% showed a poor attitude toward eye donation. Lack of knowledge regarding the process of eye donation was seen as the major cause attributing to this poor attitude. **Conclusion:** We conclude that if more intensive awareness program activities are carried out to make the younger generation, making them more aware of the process of eye donation, we can significantly increase the rate of eye donation in India.

Keywords: Corneal blindness, corneal transplantation, eye donation, non-medical students

INTRODUCTION

Global estimates state that approximately 1.3 billion people are living with some form of vision impairment.[1] As per the global data, three major causes of blindness in the world, namely cataracts, trachoma, and glaucoma, are reported.[2] In India, it is reported that the approximate number of people having vision less than 6/60 in at least one eye due to corneal diseases is 6.8 million people.[3] In the Indian scenario, corneal blindness accounts for 0.9% of blindness.[4] Corneal blindness is estimated to be the second most prevailing cause of blindness in many less developing nations.[5] A Corneal Opacity Rural Epidemiological (CORE) study done on the north Indian population showed that the prevalence of corneal disease was 3.7% (95% CI 3.4% to 4.1%) and that of corneal blindness was 0.12% (95% CI 0.05% to 0.17%).[6] Diseases responsible for corneal blindness include trachoma, onchocerciasis, leprosy, ophthalmia neonatorum, and xerophthalmia.[2] The epidemiology of corneal blindness is complicated and encompasses a wide variety of infectious and inflammatory eye diseases that cause corneal scarring, which ultimately leads to functional blindness.[7]

Gnaneswaran Subramaniam, Murugan Kumarasamy[1], Ameenah A. H. Siraja[1]

Department of Ophthalmology, Karpaga Vinayaga Institute Medical Sciences and Research Center, Maduranthakam, Tamil Nadu, [1]Department of Ophthalmology, ESIC Medical College and PGIMSR, Bangalore, Karnataka, India

Address for correspondence: Dr. Gnaneswaran Subramaniam, G4, Ras Rejoice Apartment, New No. 20, Krishna Puram Street, Choolaimedu, Chennai, 600 094, Tamil Nadu, India.
E-mail: gnanvas1@gmail.com

Submitted: 10-Jun-2022 **Revised:** 02-Nov-2022
Accepted: 29-Nov-2022 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	Quick Response Code
DOI: 10.4103/kjo.kjo_77_22	

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Subramaniam G, Kumarasamy M, Siraja AA. Awareness and attitude regarding eye donation among undergraduate students of an engineering institution and its implication in Tamil Nadu. Kerala J Ophthalmol 2023;35:174-8.

Visual rehabilitation by corneal transplantation is the main choice for the restoration of vision in those with corneal blindness.[8] Over the past 10 years, corneal transplantation or keratoplasty has emerged expeditiously.[9] It is the most commonly performed transplant worldwide. It restores visual function when impairment caused by corneal damage is deemed too severe to provide an acceptable quality of life in the country where it is performed.[9] The corneal transplant success relies on the availability of high-quality donor eyes. At present, a gap between the demand and supply of donor corneal tissues in the developing world is documented.[10] A recent global survey of eye banking and corneal transplantation quantified the extreme mismatch between the supply and demand of donor corneas worldwide, finding only 1 cornea available for every 70 needed.[11]

There exists a severe lacuna of eye donors in India. The reasons include less awareness among the general public and complex traditional beliefs coupled with infrastructural barriers.[12] The number of corneal transplants performed is far less than the actual requirement in India.[13] There exists a requirement of at least 20 eye bank training centers, 200 eye banks with corneal transplant facilities, and 2000 eye donation centers in the country for the fulfillment of the targets set,[14] while we found that eye donation is still an under-focused topic and especially among youth. This study aims to study the awareness and willingness to eye donation among non-medical students.

METHODS

A single-center cross-sectional study was conducted in a reputed Multi-disciplinary Institution, located in rural Tamil Nadu. Using the random sampling method, 507 participants were selected from August 2018 to March 2019. As no previous studies were providing the knowledge levels for eye donation, an assumption of prevalence was taken as 50%, and the required sample size was calculated as 400. With a non-response rate of 27%, the final sample size was 507. The following sample size formula was used:

$n = \frac{(Z_{\alpha/2})^2 P(1-P)}{d^2}$ where Z is the 95% confidence interval (1.96), d is the marginal error (4%), n is the sample size, P is the estimated proportion, and $(Z_{\alpha/2})$ is the critical value.

From the various undergraduate engineering departments, using simple random sampling the sample size was proportionally allocated for each selected department based on the strength of the class, and using the list of students from the official records, the roll numbers were selected using a simple random sampling method.

A self-administered, structured questionnaire with a close-ended questionnaire was provided to the students, with informed consent. It included questions about the students' awareness of eye donation, willingness to donate eyes, and suggestions to promote eye donation.

Among the roll numbers selected, if the respective student was occupied with some other class, they were informed through the department and asked to report on a particular date for data collection. "Awareness" was considered as having a realization about the fact that a dead individual's eyes can be utilized to give vision to those blind from corneal disease. "Knowledge" was considered as having an understanding regarding the details of different aspects of eye donation like pledging of eyes, who can donate eyes, when can eyes be donated, and what steps are to be taken after death to donate one's eyes.[15] The scores above 50% were considered as an adequate level of knowledge and below 50% were considered a low level of knowledge (using Bloom's cutoff points for KAP study modified). Descriptive analysis was carried out by mean and standard deviation for quantitative variables using IBM SPSS software (v. 22). The ethical clearance was obtained from the institutional ethical committee.

RESULTS

A total of 507 subjects were included in the analysis. The mean age of participants was 19 ± 2 years.

Males (58%) were more than females (42%). Among the study population, the majority of the students 498 (98.22%) had heard about eye donation and also about the current shortage of eye donors. Almost a quarter of the participants (25%) had the opinion that eyes are commercially available for sale. Only a meager 14.26% of participants had eye banks near their place [Table 1]. Concerning beliefs against eye donation, only less than a quarter (17.47%) of the participant's close family members had pledged to donate their eyes. Disfigurement of the face was the most common factor seen among 24.90% of participants [Table 2]. The majority of the participants had a good level of awareness about eye donation (98.4%) and good knowledge (51.5%) regarding eye donation, whereas 74% showed a poor attitude toward eye donation [Table 3]. The majority of the participants got information about eye donation through television/cinema (47.70%), followed by social media pages like Facebook/Twitter (35.10%),

Table 1: Descriptive analysis on awareness, knowledge on eye donation, and legal practices (*n*=507)

	Frequency	Percentage
Have you heard about eye donation		
Yes	498	98.22%
No	9	1.78%
Are you aware that there is a shortage of eyes for transplantation in India		
Yes	357	70.42%
No	150	29.58%
Timing of donation and removal		
When can we donate our eyes		
After death	481	96.59%
When alive	14	2.81%
Either alive or after death	3	0.60%
A person with communicable diseases can donate his/her eyes		
Yes	136	27.31%
No	362	72.69%
Which part of the eye is used for transplantation		
Cornea	338	67.87%
Whole eyeball	160	32.13%
The ideal time to remove eyes is within 6hrs after death		
Yes	446	89.56%
No	52	10.44%
Ideal place for eye retrieval is- place of death (house/hospital)		
Yes	266	53.41%
No	232	46.59%
An eye bank is a place to preserve donated eyes		
Yes	433	86.95%
No	65	13.05%
Donated eyes are used for		
Giving sight To Blind People	256	51.41%
Clinical research	6	1.20%
Both	217	43.57%
Don't know	19	3.82%
Legal and regulatory aspects	**Frequency**	**Percentage**
Are the eyes available commercially for sale		
Yes	126	25.30%
No	372	74.70%
Do you agree with buying/selling donor eyes		
Yes	175	35.14%
No	323	64.86%
Identity of the donor and recipient is not revealed		
Yes	350	70.28%
No	148	29.72%
Do you know any eye bank near your place		
Yes	71	14.26%
No	427	85.74%

newspaper (25.50%), friends and relatives (24.90%), and their family doctors (19.90%). Only a few reported direct text messaging (9.2%) [Figure 1].

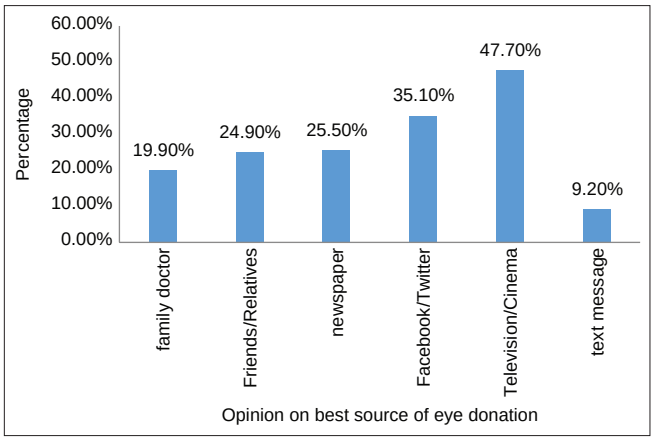


Figure 1: Bar chart of opinion on the best source of eye donation in the study population (N = 498)

DISCUSSION

In today's world, there is a global shortage of corneal transplant tissues, and failure to obtain consent from families of potential donors is a major limiting factor in tissue procurement.[16] India constitutes the world's largest corneal blindness population which makes a corneal donation one of the main requirements in India.[8] Well-organized initiatives can raise awareness among the youth about various aspects of organ donation which is necessary to eliminate the setbacks that affect the rate of availability of donor organs.[17] In order to reach toward the sustainable development goals, it is important to improve the availability of organs through donations. This study aims to improve the eye donation knowledge and awareness among the adolescent population, especially with a non-medical background.

In our study, majority of the participants (98.2%) were aware about eye donation, as compared to only 80% of the participants aware of blood donation, in a study conducted among adults in the year 2015, in rural Pondicherry.[8] This can be attributed to the study setting of our study population, which is located in a rural area, but as a university, with access to Internet and social media.

Similarly, our study showed 89% of the participants aware about the ideal time to remove eyes within 6 hours of death, which was similar to a study conducted among medical students in a tertiary hospital in Bangalore in 2015.[4] Even though the professional backgrounds were different, this can be due to the study setting with multi-disciplinary departments and hence the similarity.

Our study showed that majority (85%) of the participants did not know about any nearby eye banks, whereas 94% of participants did not know the same, in a similar study

Table 2: Beliefs and attitudes regarding eye donation (*n*=498)

Beliefs, attitudes, and practice	Frequency	Percentage
Eye donation causes disfigurement to the donor's face		
Yes	124	24.90%
No	374	75.10%
Do you have any religious beliefs against eye donation		
Yes	24	4.82%
No	474	95.18%
Any of your family members/friends have pledged to donate their eyes		
Yes	87	17.47%
No	411	82.53%

Table 3: Level of awareness, knowledge, attitude, and practice among study participants (*n*=507) toward eye donation

Level	Frequency (%)
Awareness	
Low Level	8 (1.6%)
Good Level	499 (98.4%)
Knowledge	
Poor Level	246 (48.5%)
Good Level	261 (51.5%)
Attitude and practice	
Negative Attitude	375 (74%)
Positive Attitude	132 (26%)

Majority of the participants had good level of awareness about eye donation (98.4%), whereas only half of the participants (51.5%) had good knowledge regarding eye donation. Poor attitude toward eye donation was seen in more than half of the participants (74%)

conducted in Bhopal among medical and paramedical students in 2012.[18] This shows that the level of awareness has increased tremendously in the past few years, especially among students studying in professional courses.

CONCLUSION

Our study concludes that there is an urgent need to educate the younger generation, especially the non-medical students, regarding the process of eye donation, and the ethical and legal aspects involved and sensitize them through mass media and other means. Geo-mapping of all the eye banks and eye donation centers needs to be done for a quick review and subsequent visit to the centers. Students should be regularly taken on field trips to organ donation institutions for providing hands-on knowledge about the same. Behavior change communication should be used, and the support of the local influential people can work toward improving attitudes toward eye donation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Ethical consideration

Prior Institutional ethical committee clearance was obtained for this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. World Health Organization. Blindness and vision impairment 2018. Available from: https://www.who.int/news-room/fact-sheets/detail/blindness-and-visual-impairment. [Last accessed on 2018 Oct 11].
2. Garg P, Krishna PV, Stratis AK, Gopinathan U. The value of corneal transplantation in reducing blindness. Eye (Lond) 2005;19:1106-14.
3. Gupta N, Tandon R, Gupta SK, Sreenivas V, Vashist P. Burden of corneal blindness in India. Indian J Community Med 2013;38:198.
4. Vidusha K, Manjunatha S. Awareness of eye donation among medical students of tertiary care hospital, Bangalore. Asian Pac J Health Sci 2015;2:94-8.
5. Oliva MS, Schottman T, Gulati M. Turning the tide of corneal blindness. Indian J Ophthalmol 2012;60:423-7.
6. Gupta N, Vashist P, Tandon R, Gupta SK, Dwivedi S, Mani K. Prevalence of corneal diseases in the rural Indian population: The Corneal Opacity Rural Epidemiological (CORE) study. Br J Ophthalmol 2015;99:147-52.
7. Whitcher JP, Srinivasan M, Upadhyay MP. Corneal blindness: A global perspective. Bull World Health Organ 2001;79:214-21.
8. Patil R, E RP, Boratne A, Gupta SK, Datta SS. Status of eye donation awareness and its associated factors among adults in rural pondicherry. J Clin Diagn Res 2015;9:Lc01-4.
9. Gain P, Jullienne R, He Z, Aldossary M, Acquart S, Cognasse F, *et al*. Global survey of corneal transplantation and eye banking. JAMA Ophthalmol 2016;134:167-73.
10. Singh A, Gupta N, Ganger A, Vashist P, Tandon R. Awareness regarding eye donation in an urban slum population: A community-based survey. Exp Clin Transplant 2018;16:730-5.
11. Williams AM, Muir KW. Awareness and attitudes toward corneal donation: Challenges and opportunities. Clin Ophthalmol 2018;12:1049-59.
12. Dass RI, Kumari M, Gohel DJ, Solanki N, Shah P. Awareness of eye donation in medical students and the myths prevalent amongst them. Int J Res Med 2016;5:75-7.
13. Singh MM, Rahi M, Pagare D, Ingle GK. Medical students' perception on eye donation in Delhi. Indian J Ophthalmol 2007;55:49-53.
14. Gupta N, Vashist P, Ganger A, Tandon R, Gupta SK. Eye donation and eye banking in India. Natl Med J India 2018;31:283-6.
15. Bhandary S, Khanna R, Rao KA, Rao LG, Lingam KD, Binu V. Eye donation-awareness and willingness among attendants of patients at various clinics in Melaka, Malaysia. Indian J Ophthalmol 2011;59:41-5.
16. Lee A, Ni MY, Luk AC, Lau JK, Lam KS, Li TK, *et al*. Trends and determinants of familial consent for corneal donation in Chinese. Cornea 2017;36:295-9.
17. Sam N, Ganesh R, Indrapriyadarshini V, Jeyamarthan S, Nandhini C.

Awareness, knowledge, and attitude regarding organ donation among final year students of medical, Dental, Engineering, and Arts and Science Colleges in Thiruvallur and Chennai City, India. Indian J Transplantat 2018;12:25.

18. Kumar S, Shukla US, Agarwal P. Awareness and knowledge on eye donation among students at Bhopal. Natl J Community Med 2012;3:685-9.

Original Article

Clinical and microbiologial profile of bacterial and fungal keratitis: A comparison of patients with and without diabetes mellitus

ABSTRACT

Aims: The aim of the study was to evaluate the predisposing factors, clinical features, causative microorganism, and response to treatment, among persons of infective keratitis, with and without diabetes mellitus and to determine differences between the two groups. **Subjects and Methods:** This prospective study enrolled 26 patients of infective keratitis who had diabetes mellitus and 52 patients without diabetes mellitus, by consecutive sampling who attended the ophthalmology department at a tertiary care institute. Detailed clinical evaluation and microbiological evaluation were done. Treatment was initiated according to clinical diagnosis. The patients were followed up at 2 weeks, 1 month, and 3 months. **Statistical Analysis Used:** Statistical testing was done using Chi-square test and Fisher's exact test for qualitative variables. Quantitative variables were expressed as means and standard deviations. The variables between the two groups were compared using Student's *t*-test and Wilcoxon test, where appropriate. Shapiro–Wilk test was used to test normality of data. Analysis was done using the SPSS software. **Results:** Urban population, monsoon season, and outdoor work were associated more commonly with microbial keratitis. Ocular trauma (69.2%) was the most common risk factor. A greater proportion of patients with diabetes (46.2%) did not have a history of ocular injury compared to those without (23.8%). Poor glycemic control increased severity of keratitis ($P = 0.023$). Redness and pain were the most common symptoms in both groups. Corneal sensations were significantly reduced in patients with diabetes mellitus. Diabetes mellitus was significantly associated with central ulcers (46.2%), hypopyon (50%) in anterior chamber, and fungal keratitis (35%). Hypopyon and depth of ulcer were significant predictors ($P = 0.018$ and 0.006) of the time taken for the infective keratitis to heal. *Pseudomonas aeruginosa* (19.2%) was the most common bacteria isolated in diabetic patients and Methicillin-sensitive *Staphylococus aureus* (10.3%) among nondiabetic patients. *Fusarium* was the most common fungus isolated among both groups. Ulcers healing with leukomatous opacities were higher, and the frequency of perforated corneal ulcers was also higher among diabetic patients ($P = 0.026$). Posttreatment visual acuity showed a statistically significant improvement only in patients without diabetes mellitus. **Conclusions:** Significant differences existed between the two groups regarding clinical and microbiologial profile. Aggressive treatment, strict glycemic control, and high index of suspicion for fungal keratitis are important in managing microbial keratitis patients with diabetes mellitus.

Keywords: Bacterial, cornea, diabetes mellitus, fungal, keratitis

INTRODUCTION

Corneal blindness is a major public health problem in India.[1] Corneal ulceration is a significant cause of corneal blindness in India and is estimated to cause 1.5–2.0 million new cases of monocular blindness every year, along with ocular trauma.[2] According to the National blindness and Visual Impairment Survey India 2015–2019, majority cases of blindness among

Jincy Mariya Paul, P. T. Jyothi[1]

Department of Ophthalmology, Government Medical College, Thrissur, [1]Department of Ophthalmology, Government Medical College, Kozhikode, Kerala, India

Address for correspondence: Dr. Jincy Mariya Paul, Mananthan House, Nehru Nagar 2nd Avenue, Kunnamkulam, Thrissur - 680 503, Kerala, India.
E-mail: dr.jmpaul92@gmail.com

Submitted: 20-Apr-2021 **Accepted:** 12-Jul-2021 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	Quick Response Code
DOI: 10.4103/kjo.kjo_92_21	

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Paul JM, Jyothi PT. Clinical and microbiologial profile of bacterial and fungal keratitis: A comparison of patients with and without diabetes mellitus. Kerala J Ophthalmol 2023;35:179-86.

0–49 years age group were due to nontrachomatous corneal blindness (37.5%). Over the years, the prevalence of blindness has reduced considerably, and corneal blindness has emerged as the second important cause of blindness.[1,3] The annual incidence of corneal ulcers was estimated as 1130 per million population in Madurai District of South India.[4] A study from south India reported that more than 50% of the bacterial keratitis cases and more than 60% of the fungal cases had a favorable outcome.[5]

Diabetes mellitus are a metabolic disease with hyperglycemia and altered immune status of the body due to varied pathogenic mechanisms. Keratopathy is a well-described ocular complication of diabetes.[6-9] Diabetic patients are prone to develop superficial punctate keratitis, recurrent corneal erosions, persistent epithelial defects, and corneal endothelial damage.[9] Hyperglycemia also delays epithelial wound healing.[9] This increases the risk of infective keratitis in them.

Diabetes mellitus may increase the likelihood of infection, prolong duration, greatly reduce the possibility of successful drug treatment, and necessitate surgical intervention to prevent disease progression.[10] It is therefore important to identify any differences in the clinical or microbiological profile of infective keratitis between patients with and without diabetes to provide appropriate management. Several studies have reported on the epidemiology, causative microorganisms, geographical variations, risk factors, and clinical outcomes of infective keratitis.[11-14] It is important to ascertain the profile of corneal ulcers in persons with diabetes as the clinical and microbiological profile of corneal ulcers show regional variation. We designed a prospective cohort study to determine the clinical and microbiological profile of bacterial and fungal keratitis among patients with and without diabetes mellitus presenting at the ophthalmology outpatient unit in a public sector tertiary care teaching hospital in north Kerala.

SUBJECTS AND METHODS

The study protocol that used a prospective cohort design was approved by the institutional ethics committee. Patients for the study were recruited from the ophthalmology department of the study institute over a period of 12 months from April 2018 to March 2019. The study included all consecutive cases of clinically diagnosed infective keratitis, among already diagnosed diabetic patients and nondiabetic patients above 18 years of age, who presented to the department. All suspected viral and autoimmune keratitis were excluded. Infective keratitis was considered as a loss of corneal epithelium with underlying stromal infiltration associated with signs of inflammation with or without hypopyon. Chincholikar and Pal had reported *Staphylococus aureus* and *Pseudomonas aeruginosa* as the most frequently isolated aerobic organisms in case of microbial infections (diabetic foot) in diabetic patients.[15] According to Gopinathan *et al*., in 5.3% of cases, *S. aureus* was isolated, and in 9.7%, *P. aeruginosa* was isolated.[11] The sample size was estimated considering the reported prevalence of *P. aeruginosa* (9.7%) and was estimated as 26 persons with diabetes mellitus presenting with corneal ulcers and 52 persons with corneal ulcer without diabetes mellitus. Eligible subjects were enrolled in the study after obtaining informed consent.

Ophthalmic evaluation included the measurement of visual acuity (in logMAR) and detailed examination of the corneal ulcer using a slit lamp. The size of the corneal ulcer was assessed and the location, depth of the ulcer, and its margins evaluated. The presence of satellite lesions, hypopyon, and nature and size of any infiltrates was noted. Assessment of corneal sensations was assessed qualitatively using a cotton wisp. Sensations in all four quadrants of the fellow eye were assessed and recorded as normal or reduced. Reduced corneal sensations in more than 2 quadrants were considered statistically significant. Axonal degeneration of corneal nerves results from chronic hyperglycemia and occurs bilaterally. The clinical profile was recorded at first examination, at discharge (if admitted), and at each follow-up. Patients were followed up based on the progress of healing. Symptomatic relief, reduction in size of infiltrate, healing of epithelial defect, resolution of edema in the surrounding cornea, and reduction in size of hypopyon were taken as signs of healing in response to treatment. For this study, data recorded at only three follow-up visits were considered: at 2 weeks, 1 month, and 3 months.

The demographic details including age, gender, area of residence, occupation, and month of presentation of each enrolled patient were collected. Predisposing factors such as trauma, associated ocular and adnexal diseases, and prior ocular surgeries were assessed. Glycemic status, presence of any diabetes-related complications, use of any topical therapy including corticosteroids and duration of such therapy, and history of any other systemic illness were noted.

Corneal scrapings were collected from each ulcer, after instillation of proparacaine hydrochloride ophthalmic solution 0.5%, using No. 15 Bard-Parker blade/24G sterile needle under aseptic conditions, from the leading edge and base on ulcer as per common practice protocols. The collected specimens were inoculated immediately on to the surface of a blood agar plate, Sabouraud's Dextrose Agar, and smeared on to two clean glass slides for Gram staining and KOH wet mount for fungal filaments. Bacterial and fungal

cultures were done at the microbiology lab and reports duly collected and recorded. A significant positive culture report was given when one of the following was satisfied:

i. Growth of the organism in two or more media
ii. Confluent growth of a known ocular pathogen in one solid medium
iii. Growth in one medium of an organism with positive smear results or growth of the same organism in liquid media.

A negative culture report was given after 1 week of incubation for bacterial cultures and 3 weeks for fungal cultures.

Antibiotic sensitivity to commonly used antibiotics such as methicillin, vancomycin, gentamicin, amikacin, cephalosporins, and ciprofloxacin was recorded. The standardized disk diffusion method was used for antibiotic sensitivity testing. Sensitivity and resistance patterns of fungi to commonly used antifungals could not be tested due to the unavailability of such testing at the microbiology lab in the study institute. Glycemic control was ascertained from routine blood tests and glycated hemoglobin HbA1C reports.

The patient was started empirically on the treatment after obtaining an appropriate specimen for microbiological testing, depending on the clinical opinion of the treating faculty. Treatment-naïve patients, patients with ulcers <5 mm, and patients with ulcer involving <20% of corneal stroma were started on monotherapy with topical fluoroquinolones. Patients with hypopyon and ulcers more than 5 mm diameter or involving more than 20% of stroma were started on fortified ceftazidime and fortified amikacin. Patients with a history of trauma with vegetative matter were also started simultaneously on topical natamycin. Corneal ulcers of size more than 5 mm diameter or with more than 20% of stromal involvement, nonhealing ulcers even after 1 week of topical therapy, ulcers associated with complications such as impending perforation, perforated ulcers, and scleral abscess were treated with systemic antibiotics or antifungals. Antibiotics were changed according to the culture and sensitivity report. The collected data were entered into a MS Excel spreadsheet and exported to IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY, for statistical analysis. Qualitative data were expressed as frequencies and percentages. Statistical testing was done using Chi-square test and Fisher's exact test for qualitative variables, where applicable. Quantitative variables were expressed as means and standard deviations. The variables were compared between the two groups were compared using Student's *t*-test and Wilcoxon test, where applicable. Shapiro–Wilk test was used to test normality of data.

RESULTS

The demographic profile of patients included in the study is presented in Table 1. Patients with diabetes mellitus (60.88 ± 10.401) were significantly older ($P = 0.001$) than patients without diabetes mellitus (48.67 ± 15.953) in the study. The number of cases was significantly (χ^2 $P = 0.002$) higher during the monsoon months of June (15.4%) and July (15.4%). Most patients presenting with infective keratitis in both groups were engaged in outdoor occupations including household work, agricultural work, and manual labor. Trauma was a significant risk factor (χ^2 $P \leq 0.001$) for infective keratitis and was more common (χ^2 $P = 0.037$) in patients without diabetes mellitus (76.9%) as compared to those with diabetes mellitus (46.2%). The presence of injury was higher ($P = 0.01$) among males (80.40%) than females (53.10%). Associated ocular/adnexal disease was present in 30.8% of patients with diabetes mellitus and 25.6% of those without diabetes mellitus. Ocular surface disease with tear film abnormalities and dry eye disease were the most common associated ocular morbidity among those with diabetes mellitus. Table 2 shows data regarding diabetes associated features among the study group. Nearly 57.7%

Table 1: Demographic profile of subjects in the study

Demographic variables	Number of patients		
	With diabetes (n=26)	Without diabetes (n=52)	Total
Age (years)			
<20	0	2	2
21-39	1	15	16
40-64	12	24	36
>65	13	11	24
Gender			
Males	14	32	46
Females	12	20	32
Area of residence			
Urban	12	31	43
Rural	14	21	35
Season			
November-January	4	13	17
February-April	5	17	22
May-July	10	16	36
August-October	7	6	13
Occupation			
Outdoor	23	35	58
Indoor	3	17	20
Risk factors			
History of trauma			
Present	14	40	54
Absent	12	12	24
Ocular/adnexal disease			
Present	8	12	20
Absent	18	40	58

of patients presenting with infective keratitis and diabetes mellitus also had associated microvascular and macrovascular complications. Nearly 77% of them had some grade of diabetic retinopathy.

Poor glycemic control was associated with more keratitis [Figure 1].

Pain and redness were the two most common presenting symptoms among patients with (76.9% and 96.2%) and without (75% and 90.4%) diabetes, respectively.

Defective vision was a presenting symptom in only 19.2% of participants in each group, with mean visual acuity at presentation (in Log MAR) among patients with diabetes being 1.50 (SD = 0.94) and among those without diabetes being 1.35 (SD = 1.30).

A significantly large proportion of patients with diabetes mellitus presenting with infective keratitis had decreased corneal sensations [Table 3]. Culture-proven fungal keratitis was significantly associated with the presence of hypopyon (χ^2 P = 0.013).

More patients with diabetes developed a central ulcer (n = 12, 46.2%) compared to those without (n = 16, 30.8%) diabetes and had keratitis with >50% of stromal depth involved (n = 15, 57.7%) more often than those without (n = 15, 28.8%).

Methicillin-Resistant *S. aureus* was isolated only from the diabetic patients (n = 3, 11.5%). Methicillin-Sensitive *S. aureus* (n = 8, 15.4%) was the major bacteria isolated from the nondiabetic group and *P. aeruginosa* (n = 5, 19.2%) from the diabetic group [Table 4].

Fusarium was the most common fungal species isolated from both groups (11.5% and 9%) among diabetic patients and nondiabetic patients, respectively. *Aspergillus* and *Candida* species were isolated only from diabetic patients.

Antibiotic resistance rates as obtained by antibiotic susceptibility testing using disk diffusion method were higher among diabetic patients (29.2%) as compared to nondiabetic patients (12.2%) but was not statistically significant (P = 0.06) [Figures 2-4].

All diabetic patients were given empirical polytherapy, with fortified ceftazidime and fortified amikacin or a topical fluoroquinolone and natamycin or fortified ceftazidime, fortified amikacin with natamycin, whereas only 67.3% of the

Table 2: Diabetes associated data (n=26)

Diabetes related feature	Number of patients
Diabetes related complications (other than retinopathy)	
Microvascular	2
Macrovascular	16
Both	4
None	4
Diabetic retinopathy	
Absent	6
PDR	3
Mild NPDR	8
Moderate NPDR	5
Severe NPDR	4
HbA1C (%)	
<9	12
>9	14

PDR – Proliferative diabetic retinopathy, NPDR – Non-PDR, HbA1C – Glycated haemoglobin

Table 3: Corneal sensation among patients with and without diabetes mellitus (n=78)

Corneal sensation	Group			χ^2	P
	Diabetic, n (%)	Nondiabetic, n (%)	Total, n (%)		
Normal	8 (30.8)	38 (73.1)	46 (59.0)	12.823	<0.001
Decreased	18 (69.2)	14 (26.9)	32 (41.0)		
Total	26 (100.0)	52 (100.0)	78 (100.0)		

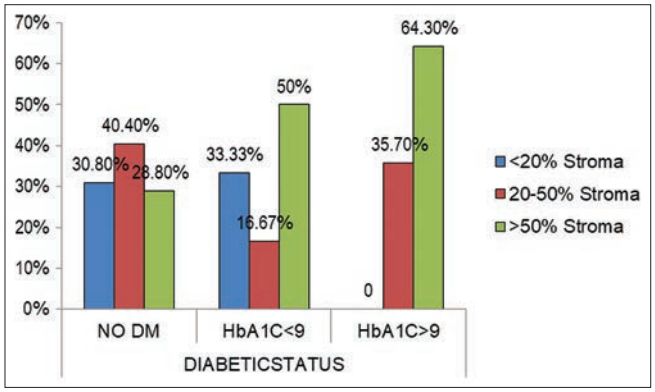


Figure 1: Glycaemic status and severity of keratitis (χ^2 = 10.873, P = 0.023)

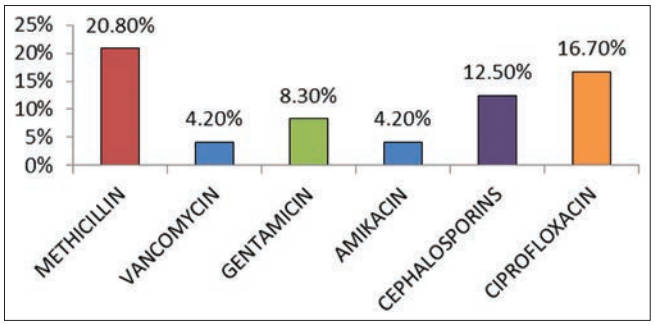


Figure 2: Resistance pattern to commonly used antibiotics

nondiabetic patients were initially treated with polytherapy ($P \leq 0.001$). A larger proportion of diabetic patients required systemic therapy with oral antibiotics (46.2%) and oral antifungals (26.9%) as compared to nondiabetic patients ($P = 0.008$) [Table 5].

Ulcers healing with leukomatous opacities were higher among the diabetic patients as well as the frequency of perforated corneal ulcers [Table 6].

Hypopyon and depth of ulcer were significant predictors ($P = 0.018$ and 0.006, respectively) of the time taken for the infective keratitis to heal [Figures 5 and 6].

Comparison between pre- and posttreatment visual acuity showed a statistically significant improvement only in patients without diabetes mellitus [Figure 7].

DISCUSSION

Persons with diabetes and infective keratitis were older compared to persons without diabetes in this study population. These results are consistent with several studies that have reported an increased association of diabetes-related complications including infective keratitis with age.[13,16] We found a higher mean age for persons with fungal keratitis and diabetes similar to a previous study[10] which reported a higher mean age for fungal keratitis among persons with diabetes. Increasing risk of infective keratitis with age may be related to the duration of diabetes, in addition to the reduced corneal nerve density and corneal sensations. We found decreased corneal sensations in persons with diabetes in this study population. This result is consistent with previous studies that have reported decreased corneal nerve density in persons with diabetes and a linear decrease in subepithelial nerve density of 0.9% per year.[17,18] The higher number of males in this study is similar to previous studies that also have reported a higher incidence among males.[19,20] The association with gender may be related to outdoor occupation and preferential access to care of males compared to females. Most of our subjects were residents of urban areas, in contrast to a study by Cao *et al*., which reported the prevalence of infective keratitis to be higher in the rural population.[21] The association with location in this study population may reflect the study location which is in an urban setting.

Most infective keratitis occurred during the monsoon season, and we did not find a statistically significant difference in the occurrence of bacterial and fungal keratitis, with season. The association with season is well recognized and

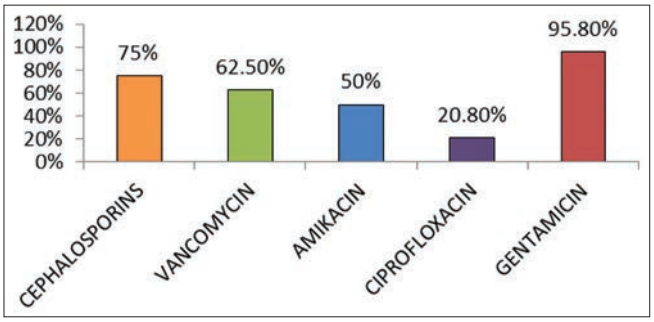


Figure 3: Sensitivity pattern to commonly used antibiotics

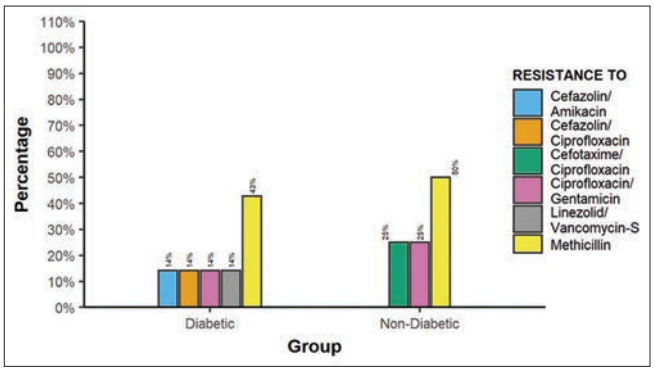


Figure 4: Common antibiotics to which resistance was obtained among diabetics vs non-diabetics ($\chi^2 = 3.654$, $P = 1.000$)

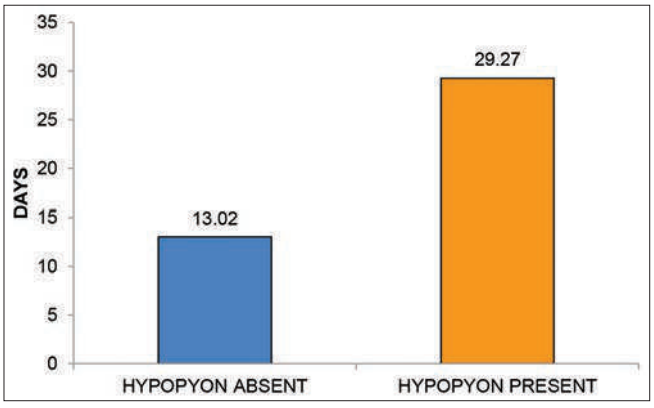


Figure 5: Association between presence of hypopyon and mean time taken for healing ($P \leq 0.001$)

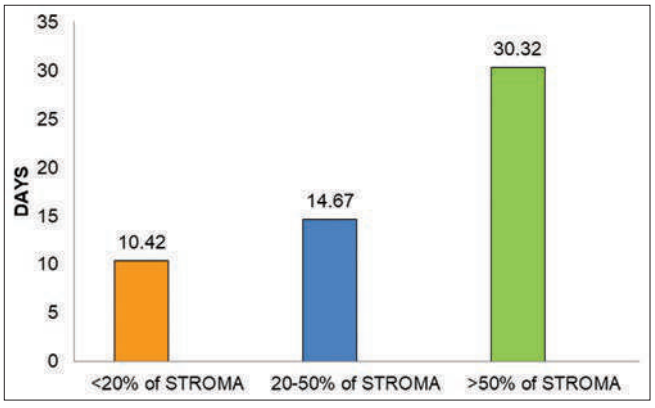


Figure 6: Association between depth of ulcer and mean time for healing ($P \leq 0.001$)

reported previously.[11,13] Wang *et al*., however, reported that the highest incidences of infectious keratopathy were observed during summer and winter, in contrast to the present study.[10] Extremes of temperature and the harvest season were associated with the observation of seasonal variation in these studies. The monsoon season in Kerala is associated with high temperatures and high humidity and is the sowing season with increased agricultural activity. The higher incidence of infective keratitis in the rainy season may be attributable partly to these environmental conditions. We found occupations involving outdoor activities (manual labor, agriculture, and household chores in homemakers) were more commonly associated with the development of infective keratitis similar to previous studies.[21,22] Ibrahim *et al*. reported a higher frequency of prior corneal injury with fungal keratitis compared to bacterial keratitis ($P < 0.0001$),[19] but we did not find a similar association in this study.

Ocular trauma was the most common risk factor in case of both bacterial and fungal keratitis as well as in both groups (diabetic patients and nondiabetic patients). There was however a significantly larger proportion of diabetic patients who reported having no history of ocular trauma. This may be either due to a previously existing ocular surface damage due to diabetic keratopathy, which may have given rise to spontaneous corneal infections without prior trauma or due to decreased corneal sensations, leading to a lack of recollection by patient of any minor trauma.

Diabetic patients who developed infective keratitis had a statistically significant association with predisposing ocular features. Wang *et al*. suggested that features of diabetic keratopathy including the delay of corneal epithelial regeneration, the decreasing of corneal sensitivity, and neurotrophic corneal ulcers were mainly caused by the changes of corneal epithelial basement membrane compositions, glycation products deposition, corneal nerve ending damage, reduced tear secretion, and oxidative stress in the hyperglycemic conditions.[23] Yoon *et al*. concluded that the corneal sensitivity, Tear Film Break-up Time, and tear secretion were significantly reduced in the diabetic patients.[24] Our study also showed decreased corneal sensitivity in the normal eye of diabetic patients which was statistically significant, and this might have been associated with diabetic keratopathy.

There was a statistically significant association between the glycemic status and the severity of keratitis in this study similar to a previous study.[25] However, Cury *et al*. have reported a lack of association of keratitis with diabetes mellitus or other comorbidities.[22] Infective keratitis may be considered to be an outcome of diabetic keratopathy with

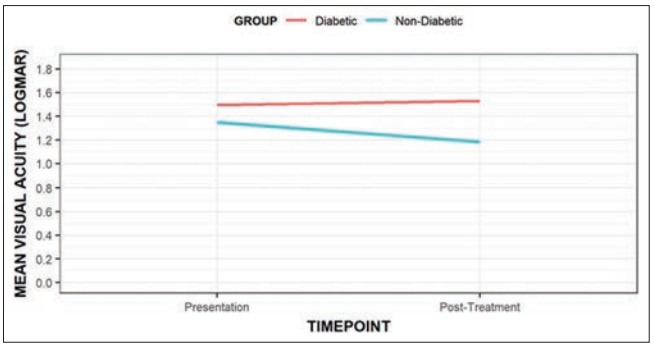


Figure 7: Trend in change in visual acuity (in LogMar) among diabetic patients and non-diabetic patients

Table 4: Association between group and bacteria isolated (*n*=78)

Bacteria isolated	Group			χ^2	*P*
	Diabetic, *n* (%)	Nondiabetic, *n* (%)	Total, *n* (%)		
None	16 (61.5)	38 (73.1)	54 (69.2)	14.396	0.005
MSSA	0	8 (15.4)	8 (10.3)		
MRSA	3 (11.5)	0	3 (3.8)		
Pneumococcus	2 (7.7)	2 (3.8)	4 (5.1)		
Psudomonas aeruginosa	5 (19.2)	3 (5.8)	8 (10.3)		
Diphtheroids	0	1 (1.9)	1 (1.3)		
Total	26 (100.0)	52 (100.0)	78 (100.0)		

MSSA – Methicillin-sensitive *Staphylococcus aureus*, MRSA – Methicillin-resistant *Staphylococcus aureus*

Table 5: Requirement for systemic therapy (*n*=78)

Systemic treatment	Group			Fisher's exact test	
	Diabetic, *n* (%)	Nondiabetic, *n* (%)	Total, *n* (%)	χ^2	*P*
None	5 (19.2)	29 (55.8)	34 (43.6)	11.035	0.008
IV antibiotic	2 (7.7)	5 (9.6)	7 (9.0)		
P/O antibiotic	12 (46.2)	10 (19.2)	22 (28.2)		
P/O antifungal	7 (26.9)	8 (15.4)	15 (19.2)		
Total	26 (100.0)	52 (100.0)	78 (100.0)		

IV – Intravenous, P/O – Per oral

Table 6: Treatment outcomes in the 2 study groups (*n*=78)

Ulcer healing	Group			Fisher's exact test	
	Diabetic, *n* (%)	Nondiabetic, *n* (%)	Total, *n* (%)	χ^2	*P*
Nonhealing	3 (11.5)	6 (11.5)	9 (11.5)	14.453	0.026
Healed with nebular opacity	2 (7.7)	11 (21.2)	13 (16.7)		
Healed with macular opacity	4 (15.4)	20 (38.5)	24 (30.8)		
Healed with leucomatous opacity	11 (42.3)	8 (15.4)	19 (24.4)		
Healed with no residual opacity	3 (11.5)	4 (7.7)	7 (9.0)		
Perforated	3 (11.5)	1 (1.9)	4 (5.1)		
Corneal melt	0	1 (1.9)	1 (1.3)		
Lost to follow-up	0	1 (1.9)	1 (1.3)		
Total	26 (100.0)	52 (100.0)	78 (100.0)		

similar pathogenic mechanisms as diabetic vasculopathies, with duration of diabetes and glycemic control being major predictive factors. An association of blood glucose levels with diabetic retinopathy is well recognized.[26] However, a similar association between glycemic status and diabetic keratopathy has not been reported yet and needs further study.

Hedayati *et al.* reported pain and redness as the most common symptoms in their study, which was similar to our findings.[27] They had reported impaired visual acuity (72.70%) and epiphora (87.90%) as common symptoms, which was in contrast to our study.

A higher proportion of diabetic patients had decreased corneal sensation in the normal eye compared to nondiabetic patients, which was statistically significant and consistent with previous studies.[28-30] Diabetic patients are predisposed to infective keratitis due to reduced corneal sensations. This can be an important target area for patient education to help prevent infective keratitis. Cruzat *et al.*, in a study using *in vivo* Confocal Microscopy, demonstrated a significant association between diminished corneal nerve densities with an increased level of inflammation[31] and may possibly explain the higher severity of keratitis among diabetic patients observed in our study.

S. aureus in persons without diabetes and *P. aeruginosa* in persons with diabetes were the most common bacterial isolates. Kaliamurthy *et al.* reported a similar finding from south India.[32] Gopinathan *et al.* have reported *Staphylococcus epidermidis* and *Corynebacterium spp*. as the most common bacteria isolated.[11] The predominance of pseudomonas in this study may have been due to the inclusion of diabetic patients. Toniolo *et al.* suggested a higher prevalence of Gram-negative bacilli such as Pseudomonas among diabetic patients.[33] *Fusarium* spp. was the most common fungal isolate among both diabetic patients and nondiabetic patients and was comparable to a previous study.[34]

Toniolo *et al.* suggested a higher incidence of antimicrobial resistance among diabetic population probably attributed to prolonged and more rampant usage of antimicrobials.[33] Our study also demonstrated a slightly higher frequency of antimicrobial resistance among patients with diabetes mellitus [Figure 4]. Resistance to methicillin and ciprofloxacin was prominent in this study [Figure 2]. Ciprofloxacin resistance may be attributed to its increased use for monotherapy in most cases of bacterial keratitis and conjunctivitis.[35,36] Gentamicin was the antibiotic to which a maximum number of bacteria isolated showed sensitivity, followed by cephalosporins [Figure 3].

Altered immune function and immune cells in diabetes mellitus were suggested by Toniolo *et al.*[33] This might explain the unrestricted spread of infiltration involving the deeper stromal layers in diabetic patients, leading to severe keratitis (depth of stromal involvement >50%) and the greater requirement of systemic therapy among diabetic patients, probably due to either unresponsiveness to conventional topical antimicrobial therapy or greater occurrence of complications or progression. More severe keratitis leads to denser scars on healing, leading to greater incidence of leukomatous scars on healing among those with diabetes. Prajna *et al.*, in the modified Mycotic Ulcer Treatment Trial II, reported the presence of hypopyon to be a significant predictor for corneal perforation in fungal ulcers.[37] Hypopyon and depth of ulcer, in this study, were significant predictors for healing. The greater severity also affected the visual outcome among patients with diabetes, with significant visual acuity improvement occurring in patients without diabetes.

There is an increasing recognition of the effects of diabetes mellitus on the ocular surface environment and the entity of diabetic keratopathy.[38] The clinical behavior of infective keratitis and its evolution among diabetic patients may vary by region, population characteristics, and the underlying prevalence of diabetes and risk factors for diabetes in the population. More studies, from diverse health-care settings and locations, must be carried out to establish practice patterns for the management. There is a dearth of evidence-based information about challenges in corneal wound healing in diabetics, microbial patterns in diabetics, and other modalities of topical treatment, in the Indian population.

Limitations

The study being conducted in a tertiary center, the study sample may not be representative of the general population.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. National Blindness and Visual Impairment Survey India 2015-2019 – A Summary Report. Available from: https://npcbvi.gov.in/writeReadData/mainlinkFile/File341.pdf. [Last accessed on 2021 Mar 25].
2. Whitcher JP, Srinivasan M, Upadhyay MP. Corneal blindness: A global perspective. Bull World Health Organ 2001;79:214-21.
3. Population Census of India; 2011. Available from: http://www.//2011-common/censusData2011.html. [Last accessed on

2021 Mar 25; Last updated on 2018 Nov 30].
4. Gonzales CA, Srinivasan M, Whitcher JP, Smolin G. Incidence of corneal ulceration in Madurai district, South India. Ophthalmic Epidemiol 1996;3:159-66.
5. Acharya. Delhi Infectious Keratitis Study: Update on Clinico-Microbiological Profile and Outcomes of Infectious Keratitis. Available from: http://www.jcurrophthalmol.org/article.asp?issn=2452-2325;year=2020;volume=32;issue=3;spage=249;epage=255;aulast=Acharya. [Last accessed on 2021 Mar 25].
6. Alves Mde C, Carvalheira JB, Módulo CM, Rocha EM. Tear film and ocular surface changes in diabetes mellitus. Arq Bras Oftalmol 2008;71:96-103.
7. Dogru M, Katakami C, Inoue M. Tear function and ocular surface changes in noninsulin-dependent diabetes mellitus. Ophthalmology 2001;108:586-92.
8. Inoue K, Kato S, Ohara C, Numaga J, Amano S, Oshika T. Ocular and systemic factors relevant to diabetic keratoepitheliopathy. Cornea 2001;20:798-801.
9. Skarbez K, Priestley Y, Hoepf M, Koevary SB. Comprehensive review of the effects of diabetes on ocular health. Expert Rev Ophthalmol 2010;5:557-77.
10. Wang B, Yang S, Zhai HL, Zhang YY, Cui CX, Wang JY, *et al*. A comparative study of risk factors for corneal infection in diabetic and non-diabetic patients. Int J Ophthalmol 2018;11:43-7.
11. Gopinathan U, Sharma S, Garg P, Rao GN. Review of epidemiological features, microbiological diagnosis and treatment outcome of microbial keratitis: Experience of over a decade. Indian J Ophthalmol 2009;57:273-9.
12. Gupta N, Vashist P, Tandon R, Gupta SK, Dwivedi S, Mani K. Prevalence of corneal diseases in the rural Indian population: The Corneal Opacity Rural Epidemiological (CORE) study. Br J Ophthalmol 2015;99:147-52.
13. Lin CC, Lalitha P, Srinivasan M, Prajna NV, McLeod SD, Acharya NR, *et al*. Seasonal trends of microbial keratitis in South India. Cornea 2012;31:1123-7.
14. Bharathi MJ, Ramakrishnan R, Meenakshi R, Padmavathy S, Shivakumar C, Srinivasan M. Microbial keratitis in South India: Influence of risk factors, climate, and geographical variation. Ophthalmic Epidemiol 2007;14:61-9.
15. Chincholikar DA, Pal RB. Study of fungal and bacterial infections of the diabetic foot. Indian J Pathol Microbiol. 2002;45:15-22.
16. Chidambaram JD, Venkatesh Prajna N, Srikanthi P, Lanjewar S, Shah M, Elakkiya S, et al. Epidemiology, risk factors, and clinical outcomes in severe microbial keratitis in South India. Ophthalmic Epidemiol 2018;25:297-305.
17. Niederer RL, Perumal D, Sherwin T, McGhee CN. Age-related differences in the normal human cornea: A laser scanning *in vivo* confocal microscopy study. Br J Ophthalmol 2007;91:1165-9.
18. Mocan MC, Durukan I, Irkec M, Orhan M. Morphologic alterations of both the stromal and subbasal nerves in the corneas of patients with diabetes. Cornea 2006;25:769-73.
19. Ibrahim MM, Vanini R, Ibrahim FM, Martins Wde P, Carvalho RT, Castro RS, *et al*. Epidemiology and medical prediction of microbial keratitis in southeast Brazil. Arq Bras Oftalmol 2011;74:7-12.
20. Müller GG, Kara-José N, Castro RS. Epidemiological profile of keratomycosis at the HC-UNICAMP. Arq Bras Oftalmol 2012;75:247-50.
21. Cao J, Yang Y, Yang W, Wu R, Xiao X, Yuan J, *et al*. Prevalence of infectious keratitis in Central China. BMC Ophthalmol 2014;14:43.
22. Cury ES, Chang MR, Pontes ER. Non-viral microbial keratitis in adults: Clinical and laboratory aspects. Braz J Microbiol 2018;49 Suppl 1:205-12.
23. Wang Y, Zhou Q, Xie L. Diabetic keratopathy: New progresses and challenges. Zhonghua Yan Ke Za Zhi 2014;50:69-72.
24. Yoon KC, Im SK, Seo MS. Changes of tear film and ocular surface in diabetes mellitus. Korean J Ophthalmol 2004;18:168-74.
25. Kibret T, Bitew A. Fungal keratitis in patients with corneal ulcer attending Minilik II Memorial Hospital, Addis Ababa, Ethiopia. BMC Ophthalmol 2016;16:148.
26. Giloyan A, Harutyunyan T, Petrosyan V. The prevalence of and major risk factors associated with diabetic retinopathy in Gegharkunik province of Armenia: Cross-sectional study. BMC Ophthalmol 2015;15:46.
27. Hedayati H, Ghaderpanah M, Rasoulinejad SA, Montazeri M. Clinical Presentation and Antibiotic Susceptibility of Contact Lens Associated Microbial Keratitis. J Pathog 2015;2015:152767.
28. Lagali NS, Allgeier S, Guimarães P, Badian RA, Ruggeri A, Köhler B, *et al*. Reduced corneal nerve fiber density in type 2 diabetes by wide-area mosaic analysis. Invest Ophthalmol Vis Sci 2017;58:6318-27.
29. Saito J, Enoki M, Hara M, Morishige N, Chikama T, Nishida T. Correlation of corneal sensation, but not of basal or reflex tear secretion, with the stage of diabetic retinopathy. Cornea 2003;22:15-8.
30. Pritchard N, Edwards K, Vagenas D, Shahidi AM, Sampson GP, Russell AW, *et al*. Corneal sensitivity as an ophthalmic marker of diabetic neuropathy. Optom Vis Sci 2010;87:1003-8.
31. Cruzat A, Witkin D, Baniasadi N, Zheng L, Ciolino JB, Jurkunas UV, *et al*. Inflammation and the nervous system: The connection in the cornea in patients with infectious keratitis. Invest Ophthalmol Vis Sci 2011;52:5136-43.
32. Kaliamurthy J, Kalavathy CM, Parmar P, Nelson Jesudasan CA, Thomas PA. Spectrum of bacterial keratitis at a tertiary eye care centre in India. BioMed Res Int 2013;2013:181564.
33. Toniolo A, Cassani G, Puggioni A, Rossi A, Colombo A, Onodera T, *et al*. The diabetes pandemic and associated infections: Suggestions for clinical microbiology. Rev Med Microbiol 2019;30:1-17.
34. Dan J, Zhou Q, Zhai H, Cheng J, Wan L, Ge C, *et al*. Clinical analysis of fungal keratitis in patients with and without diabetes. PLoS One 2018;13:e0196741.
35. Sharma V, Sharma S, Garg P, Rao GN. Clinical resistance of Staphylococcus keratitis to ciprofloxacin monotherapy. Indian J Ophthalmol 2004;52:287-92.
36. Dalhoff A. Global fluoroquinolone resistance epidemiology and implictions for clinical use. Interdiscip Perspect Infect Dis 2012;2012:976273.
37. Prajna NV, Krishnan T, Rajaraman R, Patel S, Shah R, Srinivasan M, *et al*. Predictors of corneal perforation or need for therapeutic keratoplasty in severe fungal keratitis: A secondary analysis of the mycotic ulcer treatment trial II. JAMA Ophthalmol 2017;135:987-91.
38. Shukla P, Agarwal B, Borah E, Deori N. Complicated diabetic keratopathy: A case report. Off Sci J Delhi Ophthalmol Soc 2020;30:69-71.

Original Article

Blind spot in ultrasound central corneal thickness measurement – Central corneal thickness of apex versus central corneal thickness of vertex

ABSTRACT

Aims: This study aimed to compare central corneal thickness (CCT) using ultrasound pachymetry (USP) (CCT apex) and specular microscopy (CCT vertex) and also to find out the intra-reading variability from the two instruments. **Settings and Design:** A prospective, observational study was conducted in a tertiary eye care center in southern India. **Materials and Methods:** This study was conducted on 12 patients (24 eyes, 96 data set eyes, 768 data points in total) aged 20–50, in non-pathological corneas. Eight CCT measurements by specular microscopy and eight measurements by USP were taken by two different experienced observers on day 1, followed by repeating the same on day 2. **Statistical Analysis:** The readings were averaged and compared by paired *t*-test. SPSS software was used for statistical analysis. Variability between the eight readings produced by the same instrument was calculated and coefficient of variation was plotted. Inter-examiner variability and intra-examiner variability of the two modalities were studied, and it was considered statistically significant if $P < 0.05$. **Results:** The mean CCT by USP was 522.71 μm and the mean CCT by specular microscopy was 519.43 μm. The coefficient of variation of the eight readings varied significantly between the machines. On an average, the coefficient of variation was 0.4% compared to 0.8% in specular microscopy and USP, respectively. **Conclusion:** The intra-reading variability of ultrasound CCT is twice as that compared to specular microscopy. The clinical relevance of this spread is relevant and important in modern-day practice. Hence, it is better advisable that CCT readings from both the modalities, not be used interchangeably.

Keywords: Blind Spot In Ultrasound Pachymetry, Central Corneal Thickness Apex, Central Corneal Thickness Vertex, Intra-Reading Variability, Specular Microscopy, Ultrasound Pachymetry

INTRODUCTION

There are numerous methods to measure the central corneal thickness (CCT) from the two different centers of the cornea, i.e., the corneal apex and the corneal vertex [Figure 1]. The corneal apex CCT is measured by using the pupillary center (through the optical axis) as a landmark in devices such as ultrasound pachymetry (USP), whereas the corneal vertex CCT is measured by using a fixation target and aligning the corneal vertex with the visual axis by Purkinje image method in devices such as specular microscopy.

Although USP is the gold standard, literature revealed that there were potential blind spots in the methodology of studies involving USP; such as improper mentioning of the identification of the center of the cornea and improper description regarding the orientation or placement of the

Prasanna Venkatesh Ramesh, Sathyan Parthasarathi[1], Abhinay Ashok[2], Rajesh Kumar John[3]

Medical Officer, Department of Glaucoma and Research, Mahathma Eye Hospital Private Limited, Tiruchirappalli, Tamil Nadu, [1]Director, Sathyan Eye Care Hospital and Coimbatore Glaucoma Foundation, Coimbatore, Tamil Nadu, [2]Consultant, Abhi Nethra Eye Care, Udupi, Karnataka, [3]Biostatistician, Sathyan Eye Care Hospital and Coimbatore Glaucoma Foundation, Coimbatore, Tamil Nadu, India

Address for correspondence: Dr. Prasanna Venkatesh Ramesh, Mahathma Eye Hospital Private Limited, No. 6, Tennur, Seshapuram, Tiruchirappalli - 620 017, Tamil Nadu, India.
E-mail: email2prajann@gmail.com

Submitted: 10-Jan-2021 **Revised:** 11-Feb-2021
Accepted: 06-Mar-2021 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	Quick Response Code
DOI: 10.4103/kjo.kjo_42_21	

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Ramesh PV, Parthasarathi S, Ashok A, John RK. Blind spot in ultrasound central corneal thickness measurement – Central corneal thickness of apex versus central corneal thickness of vertex. Kerala J Ophthalmol 2023;35:187-93.

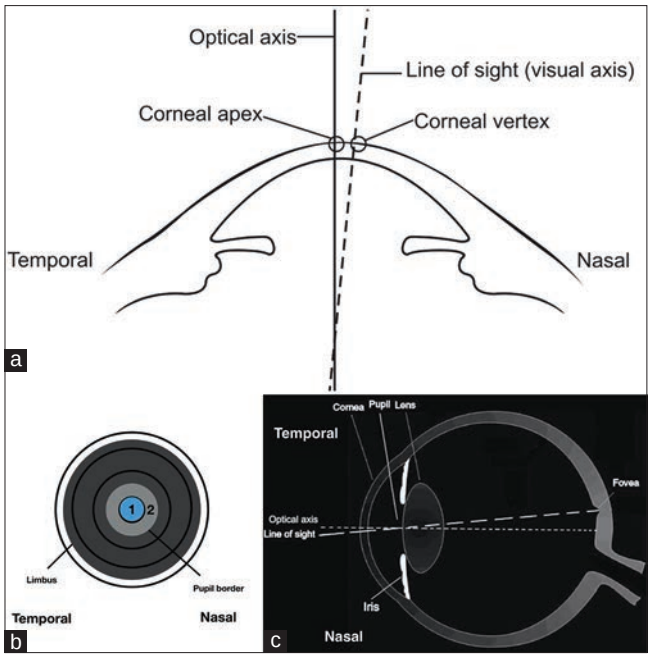


Figure 1: (a) Centers of the cornea – Corneal apex and corneal vertex. (b and c) Corneal vertex aligned with the visual axis (2) is present nasal to the corneal apex aligned with the optical axis (1)

probe; and some studies even ended up citing a previous study for their methodology without proper scientific backup.[1-3] A significant yet thought-provoking point was, the investigator seemed to visually locate the center, for placing the probe during CCT measurement from the corneal apex, which can lead to bias [Figure 2a and b].

Therefore, in this prospective study, CCT measurements of the fully automated non-contact specular microscopy (NCSM) (CCT vertex) were compared with CCT measurements of the manually assisted ultrasonic pachymetry (CCT apex). Intra-reading variability among the eight readings taken from the same machine was also tested for both the modalities. To our knowledge, this is the first study to test the intra-reading variability. Inter-examiner and intra-examiner variability was also studied.

MATERIALS AND METHODS

A prospective observational study was conducted in a tertiary care eye hospital in South India in accordance with the tenets of the Declaration of Helsinki in December 2019. Twelve consenting, consecutive patients, aged 20–50 years of age with non-pathological eyes and virgin corneas, attending ophthalmology outpatient department, were included in the study. The sample size was calculated based on previous studies comparing CCT of USP and specular microscopy.[4] Considering an alpha error of 0.05 and statistical power of 95%, 768 data sets were required. As the 12 patients (i.e., 24 eyes) were examined four times; i.e., one time by examiner A on day 1, one time by examiner B on day 1, one time by examiner A on day 2, and one time by examiner B on day 2, there were a total of 96 dataset eyes. Finally in total, as eight CCT readings were obtained with USP and eight CCT readings were obtained with specular microscopy from a single eye, (96 × 8) 768 data points were available for analysis from each category respectively.

Informed written consent was obtained from each participant. Patients with previous ocular surgery, previous refractive procedure, corneal ectasias, glaucoma, on topical medication for any ocular condition, one-eyed patients, uncontrolled diabetes mellitus, corneal pathologies such as dystrophies, degeneration, microcornea, iridocorneal endothelial syndrome, and those who did not give consent were excluded. A detailed history and examination was carried out. Visual acuity by Snellen chart, anterior segment (AS) examination by slit lamp, and fundus examination by 78D/90D/direct ophthalmoscope were carried out followed by the NCSM and finally the contact USP for CCT.

Day-one examination

On day 1, first, the NCSM was performed by both the investigators, A and B, followed by the contact USP. Eight specular CCT readings were obtained by examiner A for both eyes separately, following which eight specular CCT readings were obtained by examiner B for both eyes separately. Then after applying proparacaine (0.5%) eye drops to both eyes and after waiting for 5 min, eight CCT readings were obtained with USP by examiner A for both eyes individually while asking the patient to fixate on a target at 6 metres, following which eight CCT readings were obtained with USP by examiner B for both eyes individually while asking the patient to fixate on the same target. All CCT examinations were done between 10 am and 11 am in the morning to avoid diurnal fluctuation of CCT influencing the obtained readings. In addition, each examiner was masked of the values from the other.

Day-two examination

On day 2, similarly, first, NCSM was performed by both the investigators, A and B, followed by USP. Eight readings were obtained by A and B independently for both USP and NCSM between 10 am and 11 am. In addition, each examiner was masked of the values from the other.

Ultrasound pachymetry

USP was determined using A-scan (DGH technology, Inc, Pachette 2, USA). Prior to taking the measurement, the ultrasound pachymeter was calibrated according to the manufacturer's instruction manual. A-scan velocity was set at 1640 m/s for all the measurements and then tested with

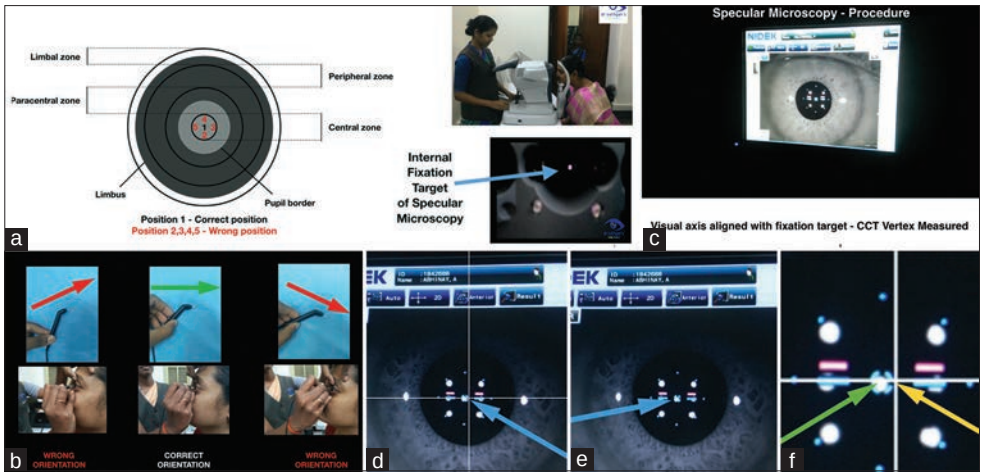


Figure 2: Probe positioning on the cornea. (a) Correct probe position (Position 1). Wrong probe position (Positions 2,3,4, and 5). (b) Correct and wrong orientation of the probe on the cornea. (c) Central corneal thickness vertex measurement in specular microscopy using internal fixation target. (d) Corneal apex (blue arrow). (e) Corneal vertex (blue arrow). (f) Corneal vertex (green arrow) present nasal to the corneal apex (yellow arrow)

an appropriate test block.[5] Topical anesthesia used was proparacaine hydrochloride 0.5% eye drops. The patient was made to sit upright and was asked to look straight ahead and fixate on a target at 6 m. The handheld probe was placed perpendicularly on the center of the cornea, which was visually located by the investigator. All measurements of USP in the study were performed by two investigators, A and B, experienced in the use of device. Eight readings were obtained. Values with a standard deviation (SD) of 5 µm or less were considered suitable for inclusion.[6] The probe was sterilized with alcohol after using it for each patient.

Non-contact specular microscopy

A non-contact specular microscope (CEM-530; NIDEK CO., LTD., Japan) was used to obtain the CCT measurement [Figure 2c]. The participant's head was positioned against the headrest and chin rest. They were instructed to look straight ahead at the fixation target. Images of the central corneal area were captured after proper positioning of the alignment dot circle bar of the screen, with the Purkinje image of the cornea. CCT analyses were carried out automatically with the retracing method using the manufacturer's built-in image analysis software. All measurements of NCSM in the study were performed by two investigators, A and B, experienced in the use of device.

Statistical analysis

The readings were averaged and compared by paired *t*-test. As eight CCT readings were obtained with USP and eight CCT readings were obtained with NCSM from a single eye, (96 × 8) 768 data points were available for analysis. SPSS (Statistical Package for Social Sciences version 20, IBM, USA) software version 17.0 was used for statistical analysis. To evaluate the agreement between the two methods, we calculated 95% limits of agreement and visually depicted it using a Bland–Altman plot [Figure 3a]. Variability between the eight readings produced by the same instrument was calculated; and coefficient of variation was plotted [Figure 3b] and compared with one another. Inter-examiner variability and intra-examiner variability of the two modalities were also studied by the paired *t*-test and was considered statistically significant if $P < 0.05$.

RESULTS

Central corneal thickness apex (ultrasound pachymetry) versus central corneal thickness vertex (non-contact specular microscopy)

The mean CCT by USP was 522.71 µm and the mean CCT by NCSM was 519.43 µm [as shown in Table 1]. The mean CCT by two machines varied only by 3.28 µm. Table 1 also reveals the descriptive statistical analysis of various CCT subgroups.

Intra-reading variability of ultrasound pachymetry central corneal thickness versus non-contact specular microscopy central corneal thickness

The coefficient of variation of the eight readings, i.e., the intra-reading variability, varied significantly between the two machines. On an average, the coefficient of variation was 0.4% compared to 0.8% in specular microscopy and USP, respectively [Figure 3b]. One percent of variation would indicate a 5.2 µm from the mean CCT if mean CCT is 520 µm on both sides (SD).

Bland–Altman plot was plotted to visually depict the limits of agreement of CCTs between the two modalities [Figure 3a].

Inter-examiner variability

Table 2 reveals the inter-examiner variability with their paired differences. There was a statistically significant difference

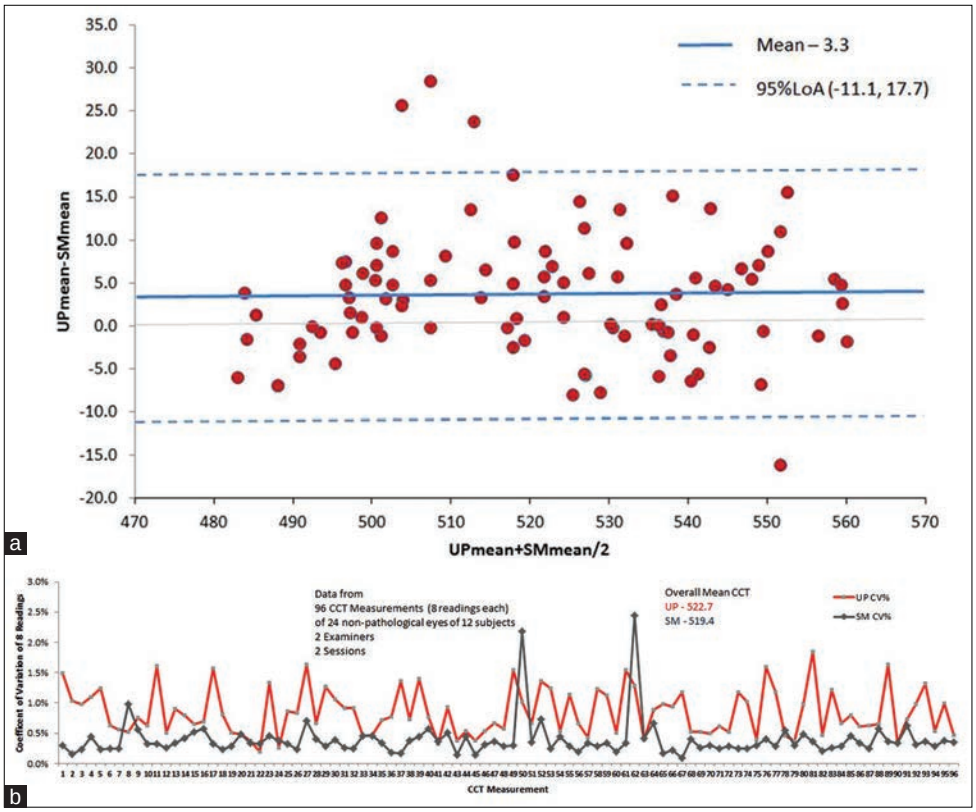


Figure 3: (a) Bland–Altman plot visually depicting the limits of agreement between central corneal thickness by two different modalities (ultrasound pachymetry and specular microscopy). (b) Coefficient of variation of the eight central corneal thickness readings (intra-reading variability) from the two different modalities; red graph – ultrasound pachymetry; gray graph – specular microscopy

Table 1: Descriptive statistical analysis of the central corneal thickness measurements (μm) performed by two separate examiners on two separate days

CCT	Mean±SD (μm)
SA1 CCT (n=192)	520.44±22.36
SB1 CCT (n=192)	518.43±21.98
SA2 CCT (n=192)	519.51±21.86
SB2 CCT (n=192)	519.18±21.78
PA1 CCT (n=192)	522.92±20.82
PB1 CCT (n=192)	524.20±22.36
PA2 CCT (n=192)	522.02±21.25
PB2 CCT (n=192)	521.76±22.90
Specular CCT (total n=768)	519.43±21.73
Ultrasound CCT (total n=768)	522.71±22.09

CCT – Central corneal thickness, A1 – Examiner A on 1st day, B1 – Examiner B on 1st day, A2 – Examiner A on 2nd day, B2 – Examiner B on 2nd day, SA1 – Specular CCT value by examiner A on 1st day, SA2 – Specular CCT value by examiner A on 2nd day, SB1 – Specular CCT value by examiner B on 1st day, SB2 – Specular CCT value by examiner B on 2nd day, PA1 – Ultrasound pachymetry CCT value by examiner A on 1st day, PA2 – Ultrasound pachymetry CCT value by examiner A on 2nd day, PB1 – Ultrasound Pachymetry CCT value by examiner B on 1st day, PB2 – Ultrasound pachymetry CCT value by examiner B on 2nd day

between examiners A and B for ultrasound CCT on day 1. There was no statistical significance between examiners A and B for ultrasound CCT on day 2. There was no statistical significance between examiners A and B for specular CCT on neither day 1 nor day 2.

Intra-examiner variability

Table 2 reveals the intra-examiner variability with their paired differences. There was no statistically significant difference between specular CCT on day 1 and 2 by neither examiner A nor examiner B, whereas between ultrasound CCT on day 1 and day 2 by examiner A and between ultrasound CCT on day 1 and day 2 by examiner B, the difference was statistically significant.

DISCUSSION

Corneal thickness is an important and sensitive indicator of corneal health.[7] It is useful in evaluating corneal barrier and endothelial pump function, monitoring corneal diseases such as corneal edema and keratoconus, and selecting patients for refractive surgery.[8,9] In clinical practice, it is useful in the evaluation of contact lens wear and dry eye therapy.[4,10] Furthermore, CCT is a significant risk factor for progression of ocular hypertension to primary open angle glaucoma, thus an important parameter in the risk profiling of ocular hypertensives and glaucoma patients.[11,12] CCT is also a predictive factor for glaucoma progression in patients with higher baseline intraocular pressure (IOP). Since IOP measurement by applanation tonometry is influenced by CCT, it is important to obtain the reliable corneal pachymetry

Table 2: Paired sample t-test for inter-examiner variability analysis reveals pair 1, 2, and 4 are statistically not significant. Pair 3 is statistically significant (P<0.05). Paired sample t-test for intra-examiner variability analysis reveals pair 1 and 2 are statistically not significant. Pair 3 and 4 are statistically significant (*P* value less than 0.05)

Inter-examiner analysis	Paired differences				*P*
	Mean of difference	SD	95% CI of the difference		
			Lower	Upper	
Pair 1: SA1-SB1	2.01	4.45	0.13	3.88	0.360
Pair 2: SA2-SB2	0.32	1.45	−0.29	0.93	0.288
Pair 3: PA1-PB1	−1.29	6.75	−4.13	1.56	0.037
Pair 4: PA2-PB2	0.27	7.78	−3.02	3.55	0.869
Intra-examiner analysis	**Paired differences**				***P***
	Mean of difference	**SD**	**95% CI of the difference**		
			Lower	**Upper**	
Pair 1: SA1-SA2	0.93	8.44	−6.04	1.08	0.164
Pair 2: SB1-SB2	−0.75	8.40	−9.33	−2.23	0.065
Pair 3: PA1-PA2	0.90	5.53	−4.85	−0.17	0.036
Pair 4: PB1-PB2	2.44	6.49	−5.31	0.17	0.003

CI – Confidence interval, SD – Standard deviation, CCT – Central corneal thickness, A1 – Examiner A on 1st day, B1 – Examiner B on 1st day, A2 – Examiner A on 2nd day, B2 – Examiner B on 2nd day, SA1 – Specular CCT value by examiner A on 1st day, SA2 – Specular CCT value by examiner A on 2nd day, SB1 – Specular CCT value by examiner B on 1st day, SB2 – Specular CCT value by examiner B on 2nd day, PA1 – Ultrasound pachymetry CCT value by examiner A on 1st day, PA2 – Ultrasound pachymetry CCT value by examiner A on 2nd day, PB1 – Ultrasound Pachymetry CCT value by examiner B on 1st day, PB2 – Ultrasound pachymetry CCT value by examiner B on 2nd day

for each patient with glaucoma and adjust the IOP for the measured CCT.[1,6]

Currently, USP is viewed as the gold standard.[12,13] It is a contact procedure which measures the CCT from the apex with the investigator visually locating the center of the cornea. It requires contact with the cornea and uses the ultrasound principle to determine thickness.[4] Although USP has remained the gold standard for measurement of CCT, there are many newer modalities such as Orbscan, Pentacam, AS-optical coherence tomography, and specular microscopy which have widened the options and introduced further accuracy.[14]

Specular microscopy used in our study is an automated procedure where the investigator has a very minimal role to play. NCSM with Nidek CEM 530 (NIDEK CO., LTD., Japan) specular microscope is a new non-contact optical instrument that provides pachymetry measurements from the vertex (CCT vertex) and specular microscopic examination simultaneously. Measurement of corneal thickness by specular microscopy requires differential focusing on the epithelial and endothelial cell density.

Central corneal thickness apex versus central corneal thickness vertex

The corneal vertex (which intersects the visual axis) is slightly nasal compared to the corneal apex (which intersects the optical axis), as shown in Figure 1. The difference between CCT measured between the two centers in this study was 3.28 µm, with CCT apex from USP being higher than CCT vertex from NCSM. A review of literature revealed that the CCT apex obtained using USP has given systematically higher values than the CCT vertex using specular microscopy.[4] In these recent papers, specular microscopy CCT measurements were found to be thinner than USP by 32 µm,[4] 28 µm,[15] 0.98 µm,[16] 19.4 µm,[17] and 21.4 µm.[18] One important observation is that the difference between CCT apex and CCT vertex can be as minimal as less than 1 µm in non-pathological eyes, as the corneal vertex and the apex are very close to each other [Figure 2d-f]. Hence in clinical practice, the CCT values can be taken from any one of the centers in non-pathological eyes.[9]

In this study, the possible reason for CCT measurement of USP (CCT apex) to be higher than NCSM (CCT vertex) may be due to the influence of local anesthetic agent or the unlikely human error in placement of the probe while performing CCT with USP. Local anaesthetics can modify Na+/K+ ATPase activity on corneal endothelium and corneal osmotic pressure; and consequently increase the corneal stromal hydration, thus increasing the CCT.[19-21] Also, however experienced the investigator may be, due to parallax error, a slight off-axis placement of the probe in the peripheral cornea will give an erroneously higher reading than the center of the cornea. This human error is not possible in the fully automated NCSM which follows the Purkinje image method guided by an internal fixation target.

Intra-reading variability of ultrasound central corneal thickness versus specular microscopy central corneal thickness

CCT measurements obtained by the NCSM showed better intra-reading variability coefficient (±2.08 µm) than those by USP (±4.16 µm). When the same was expressed as a percentage, they were 0.4% and 0.8% for NCSM and USP, respectively [Figure 3b]. The intra-reading variability coefficient of USP CCT is twice as that compared to NCSM. Furthermore, the intra-reading variability of USP in this study was consistently higher than those of NCSM in each session and between sessions, suggesting that CCT measurements by NCSM were more reliable. According to our knowledge, this is the first paper to highlight this variability (intra-reading variability). Previously, there were papers on intra-session, inter-session, intra-observer, inter-observer variability of CCT but none on the intra-reading variability. So far, this has somehow fallen in our blind spot.

Inter-examiner variability

There was a statistically significant difference between examiners A and B for ultrasound CCT on day 1. There was no statistical significance between examiners A and B for ultrasound CCT on day 2. This can be explained by the manual selection of USB probe placement. Though however experienced the examiner may be, it is very difficult for him to place the probe on the same exact spot on all eight occasions. There is no statistical significance between examiners A and B for specular CCT on day 1 and 2, respectively. This can be explained by the automated reading taken with the help of an internal fixation target, focusing the Purkinje image consistently on the same spot on the corneal vertex for performing the test.

The repeatability coefficient for the NCSM was better than USP for both examiners A and B. The 95% limits of repeatability (LoR) were between −6 and 1 μm and −9 and −2 μm for the first and second observer, respectively, in this study. In a previous study, the 95% LoR was between −15 and 17 μm and −18 and 18 μm for the first and second observer, respectively.[22] This indicates a possible improvement in precision of the newer design of NCSM used in this study.[23] A few other studies have expressed coefficient of repeatability as a percentage; however unfortunately, because the cited papers did not provide the method of calculating the repeatability coefficient as a percentage, it is impossible to make a direct comparison.[24-26]

Intra-examiner variability

There is no statistically significant difference between specular CCT on day 1 versus 2 by neither examiner A nor examiner B, whereas between ultrasound CCT on day 1 versus day 2 by examiner A and between ultrasound CCT on day 1 versus day 2 by examiner B, the difference was statistically significant. Intra-examiner variability is inconsistent in the ultrasound group, owing to more variability of ultrasound CCT readings compared to the specular CCT readings. Although specular microscopy is not the gold standard, the repeatability of the specular microscope is comparable to USP for CCT measurement and highly reliable.[23] This study confirms the same. The repeatability coefficient for NCSM was better in both the sessions than for the USP (±2 μm vs. ± 4 μm in session 1 and ± 2 μm vs. ± 4 μm in session 2) in this study. The LoR in another study with NCSM was −10 and 10 μm and −8 and 8 μm for the first and second session, respectively, indicating the possible newer design of NCSM used in this study with minimal operational error.[23]

A review of literature revealed that both intra-examiner variability and inter-examiner variability with USP were extremely high due to the fact that USP does not have a fixation light, and the diameter of probe is only 1 mm (which may have induced some variation while positioning on the cornea manually). In addition, further potential source of variability lies in the corneal touch technique.[27] A variation of >15 μm is observed in 11.3% of intra-examiner evaluations and 22% of inter-examiner evaluations. This indicates that care should be taken in the interpretation of IOP measurement corrected for CCT obtained using USP. In fact, it is possible to expect 10% of the CCT measurements to induce an incorrect IOP estimate of about 1 mmHg, even when the same operator performs the CCT examinations.[27]

This study shows that multiple readings taken with the NCSM would be more useful for comparisons over time in situations where a patient needs to be followed up over a period of time.[28] Nevertheless, in conditions of cornea cloudiness or media opacities, the USP is the method of choice in measurement of CCT over optically based pachymeters.

Limitation and suggestions

Major limitation of this study should be acknowledged. Only non-pathological virgin corneas were involved in the study. To compensate for this, future studies should be done on eyes with corneal pathologies such as corneal ectasias and keratoconus. In non-pathological eyes, the corneal vertex and the apex are very close to each other and can be used interchangeably in clinical practice, whereas in pathological eyes like keratoconus, the corneal vertex and apex are further from one another. Hence, the clinical application and relevance of the CCT apex and CCT vertex in pathological conditions need to be studied.

CONCLUSION

The CCT measurement by USP gives higher values compared to NCSM measurement. The intra-reading variability of USP CCT is twice as that compared to the intra-reading variability of specular microscopy and is statistically significant. The clinical relevance of this spread is important in routine modern-day clinical practice, especially glaucoma practice, for interpretation of IOP measurement corrected for CCT obtained. Hence, it is better advisable that CCT readings from both the modalities not be used interchangeably.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Sadoughi MM, Einollahi B, Einollahi N, Rezaei J, Roshandel D, Feizi S. Measurement of central corneal thickness using ultrasound pachymetry and Orbscan II in normal eyes. J Ophthalmic Vis Res 2015;10:4-9.
2. Rashid RF, Farhood QK. Measurement of central corneal thickness by ultrasonic pachymeter and oculus pentacam in patients with well-controlled glaucoma: Hospital-based comparative study. Clin Ophthalmol 2016;10:359-64.
3. Luo YH, Zhong Q, Ouyang PB, Guo XJ, Duan XC. Repeatability and agreement of CCT measurement in myopia using entacam and ultrasound pachymetry. Int J Ophthalmol 2012;5:329-33.
4. Bovelle R, Kaufman SC, Thompson HW, Hamano H. Corneal thickness measurements with the Topcon SP-2000P Specular Microscope and an ultrasound pachymeter. Arch Ophthalmol 1999;117:868-70.
5. Wong AC, Wong CC, Yuen NS, Hui SP. Correlational study of central corneal thickness measurements on Hong Kong Chinese using optical coherence tomography, Orbscan and ultrasound pachymetry. Eye (Lond) 2002;16:715-21.
6. Doughty MJ, Zaman ML. Human corneal thickness and its impact on intraocular pressure measures: A review and meta-analysis approach. Surv Ophthalmol 2000;44:367-408.
7. Ortiz S, Mena L, Rio-San Cristobal A, Martin R. Relationships between central and peripheral corneal thickness in different degrees of myopia. J Optom 2014;7:44-50.
8. O'Neal MR, Polse KA. *In vivo* assessment of mechanism controlling corneal hydration. Invest Ophthalmol Vis Sci 1985;26:849-56.
9. Li Y, Tang M, Zhang X, Salaroli CH, Ramos JL, Huang D. Pachymetric mapping with Fourier-domain optical coherence tomography. J Cataract Refract Surg 2010;36:826-31.
10. Guzey M, Satici A, Karaman SK, Ordulu F, Sezer S. The effect of topical cyclosporine A treatment on corneal thickness in patients with trachomatous dry eye. Clin Exp Optom 2009;92:349-55.
11. Gordon MO, Beiser JA, Brandt JD, Heuer DK, Higginbotham EJ, Johnson CA, *et al*. The ocular hypertension treatment study: Baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol 2002;120:714-20.
12. Ramesh PV, Parthasarathi S, John RK. Association between central corneal thickness and ocular dominance in a South Indian population. TNOA J Ophthalmic Sci Res 2021;59:13-7.
13. Gordon A, Boggess EA, Molinari JF. Variability of ultrasonic pachymetry. Optom Vis Sci 1990;67:162-5.
14. Ramesh PV, Jha KN, Srikanth K. Comparison of central corneal thickness using anterior segment optical coherence tomography versus ultrasound pachymetry. J Clin Diagn Res 2017;11:NC08-11.
15. Módis L Jr., Langenbucher A, Seitz B. Corneal thickness measurements with contact and noncontact specular microscopic and ultrasonic pachymetry. Am J Ophthalmol 2001;132:517-21.
16. Fujioka M, Nakamura M, Tatsumi Y, Kusuhara A, Maeda H, Negi A. Comparison of Pentacam Scheimpflug camera with ultrasound pachymetry and noncontact specular microscopy in measuring central corneal thickness. Curr Eye Res 2007;32:89-94.
17. Uçakhan OO, Ozkan M, Kanpolat A. Corneal thickness measurements in normal and keratoconic eyes: Pentacam comprehensive eye scanner versus noncontact specular microscopy and ultrasound pachymetry. J Cataract Refract Surg 2006;32:970-7.
18. Chaudhry IA. Measurement of central corneal thickness in health and disease. Saudi J Ophthalmol 2009;23:179-80.
19. Asensio I, Rahhal SM, Alonso L, Palanca-Sanfrancisco JM, Sanchis-Gimeno JA. Corneal thickness values before and after oxybuprocaine 0.4% eye drops. Cornea 2003;22:527-32.
20. Almubrad TM, Ogbuehi KC. Clinical investigation of the effect of topical anesthesia on intraocular pressure. Clin Ophthalmol 2007;1:305-9.
21. Chen HT, Chen KH, Hsu WM. Toxic keratopathy associated with abuse of low-dose anesthetic: A case report. Cornea 2004;23:527-9.
22. Ogbuehi KC, Almubrad TM. Repeatability of central corneal thickness measurements measured with the Topcon SP2000P specular micro- scope. Graefes Arch Clin Exp Ophthalmol 2005;243:798-802.
23. Almubrad TM, Osuagwu UL, Alabbadi I, Ogbuehi KC. Comparison of the precision of the Topcon SP-3000P specular microscope and an ultrasound pachymeter. Clin Ophthalmol 2011;5:871-6.
24. Ladi JS, Shah NA. Comparison of central corneal thickness measurements with the Galilei dual Scheimpflug analyzer and ultrasound pachymetry. Indian J Ophthalmol 2010;58:385-8.
25. Muscat S, McKay N, Parks S, Kemp E, Keating D. Repeatability and reproducibility of corneal thickness measurements by optical coherence tomography. Invest Ophthalmol Vis Sci 2002;43:1791-5.
26. Bakana Y, Gerber Y, Elbaz U, Schwartz S, Ken-Dror G, Anvi I, *et al*. Central corneal thickness measurement with the Pentacam Scheimpflug system, optical low-coherence reflectometry pachymeter, and ultra- sound pachymeter. J Cataract Refract Surg 2005;31:1729-35.
27. Miglior S, Albe E, Guareschi M, Mandelli G, Gomarasca S, Orzalesi N. Intraobserver and interobserver reproducibility in the evaluation of ultrasonic pachymetry measurements of central corneal thickness. Br J Ophthalmol 2004;88:174-7.
28. Insler MS, Baumann JD. Corneal thinning syndromes. Ann Ophthalmol 1986;18:74-5.

Original Article

Macular morphological changes in retinal vein occlusion with macular involvement and their association with macular ischemia

ABSTRACT

Aim: The aim is to study the association between macular morphological changes and macular ischemia in retinal vein occlusion (RVO) involving macula by spectral domain-optical coherence tomography (SD-OCT). **Settings and Design:** Observational cross-sectional study. **Materials and Methods:** The study included a total of 31 eyes of 30 RVO patients involving macula divided into two groups on the basis of fundus fluorescein angiography: Group A (RVO with macular ischemia) and Group B (RVO without macular ischemia). In each patient, macular cube and horizontal HD raster scans of the macula were performed to evaluate quantitative (central foveal thickness [CFT]) and qualitative (loss of inner retinal layers, loss of foveal inner segment/outer segment [IS/OS] junction, and prominent middle-limiting membrane [p-MLM] sign) macular morphological changes, respectively. **Statistical Analysis:** The continuous and categorical data were analyzed using unpaired *t*-test and Fisher's exact test, respectively, with GraphPad Prism 9 software. **Results:** The mean CFT was thinner in Group A (432.71 ± 172.30 μm) as compared to Group B (564.57 ± 151.16 μm) and the difference between the two groups was statistically significant ($P < 0.05$). In this study, we found that the loss of inner retinal layer and loss of foveal IS/OS junction were more commonly associated with the macular ischemia group and this difference was statistically significant $P = 0.0245$ and 0.0292, respectively. We did not find any significant relationship between p-MLM sign with macular ischemia. **Conclusion:** SD-OCT parameters such as CFT, loss of inner retinal layer, and loss of foveal IS/OS junction were observed to predict macular ischemia to some extent.

Keywords: Central foveal thickness, loss of inner retinal layer and loss of foveal inner segment/outer segment junction, macular ischemia, prominent middle-limiting membrane sign, retinal vein occlusion

INTRODUCTION

After diabetic retinopathy, the second-most common cause of visual loss is retinal vein occlusion (RVO) among retinal vascular diseases.[1-3]

In this study, we wish to evaluate macular morphologic changes by spectral-domain optical coherence tomography (SD-OCT) in RVO patients with and without macular ischemia to investigate whether on the basis of these macular morphologic changes, the perfusion state of the macula can be identified by SD-OCT.

Traditionally, for establishing macular ischemia, fundus fluorescein angiography (FFA) is considered the gold standard but it is an invasive technique and may result in an allergic reaction whereas, SD-OCT is a noninvasive method.

MATERIALS AND METHODS

All patients with RVO involving macula fulfilling inclusion criteria and meeting no exclusion criteria were enrolled in the study.

Renuka Rawat, Charudatt Chalisgaonkar, Divya Tripathi, Shashi Jain

Department of Ophthalmology, Shyam Shah Medical College, Rewa, Madhya Pradesh, India

Address for correspondence: Dr. Renuka Rawat, Sumati Girls Hostel, Old Doctor's Colony, Rewa, Madhya Pradesh, India.
E-mail: renuka29aug@gmail.com

Submitted: 12-Oct-2021 **Accepted:** 27-Jan-2022 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	Quick Response Code
DOI: 10.4103/kjo.kjo_201_21	

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Rawat R, Chalisgaonkar C, Tripathi D, Jain S. Macular morphological changes in retinal vein occlusion with macular involvement and their association with macular ischemia. Kerala J Ophthalmol 2023;35:194-7.

Inclusion criteria

(a) A diagnosis of RVO involving macula in at least one eye. (b) The patient was ready to participate in the study and willing to sign informed consent.

Exclusion criteria

(a) Eyes with poor quality SD-OCT scans (quality score <5 and scans where fovea could not be identified). (b) Eyes with poor fluorescein angiography images (where fovea could not be visualized due to hazy media or due to blocked fluorescence from hemorrhage). (c) Patients with macular edema caused by other etiologies such as diabetic retinopathy, postoperative cystoid macular edema, inflammatory cystoid macular edema, and chronic (>6 months) medication use like benzalkonium chloride, carmustine, etc., (d) Patients with RVO that previously got treated for the same (like administration of anti–vascular endothelial growth factor or steroid intravitreally and/or laser photocoagulation).

After taking written consent, a detailed clinical history was taken including the chief visual complaint, history of present illness, past medical, and surgical history. The clinical examination included assessment of best-corrected visual acuity (BCVA) by Snellen's chart, intraocular pressure, anterior segment examination, fundus examination, colored fundus photography (using Topcon TRC-50 DX), FFA, and OCT (using cirrus HD-OCT model 500) were performed in all included patients in this study at the time of the first presentation.

In this study, we assessed FFA images and divided all FFA images into two categories on the basis of presence or absence of macular ischemia. Macular ischemia was considered to be present when:

- Foveal avascular zones (FAZs) ≥1000 μm, or broken perifoveal capillary rings at the borders of the FAZ or distinct areas of capillary nonperfusion within one disc diameter of the foveal center.[4]

In each patient, macular cube scan and horizontal HD raster scan of the macula were performed to evaluate quantitatively central foveal thickness (CFT) and qualitatively (loss of inner retinal layers, loss of foveal inner segment/outer segment [IS/OS] junction, and prominent middle-limiting membrane [p-MLM] sign) macular morphological changes, respectively.

When IS/OS junction line was absent or disrupted at the fovea [Figure 1], such eyes were classified as having loss of IS/OS junction[5] while eyes were classified as having loss of inner retinal layer [Figure 2] when the delineation of inner retinal layers was not possible and the reflectivity of inner retinal layer was increased.[6]

p-MLM sign [Figure 3] was also evaluated with HD raster scan. The presence of p-MLM sign was considered when eyes had a hyperreflective line present at the outer border of inner nuclear layer.[6]

All the analyses were performed by trained observers.

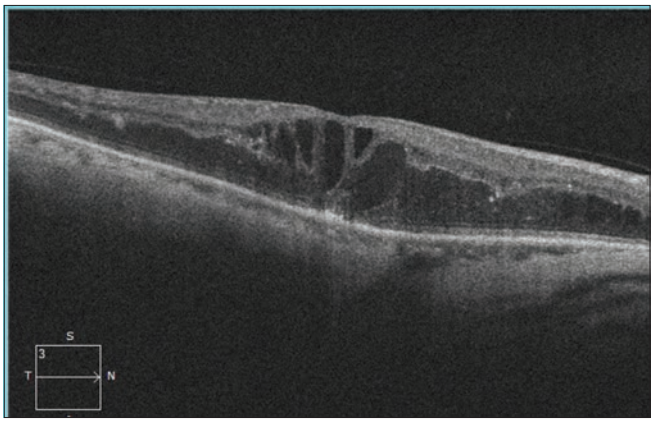


Figure 1: HD raster scan through macula showing loss of foveal inner segment/outer segment junction

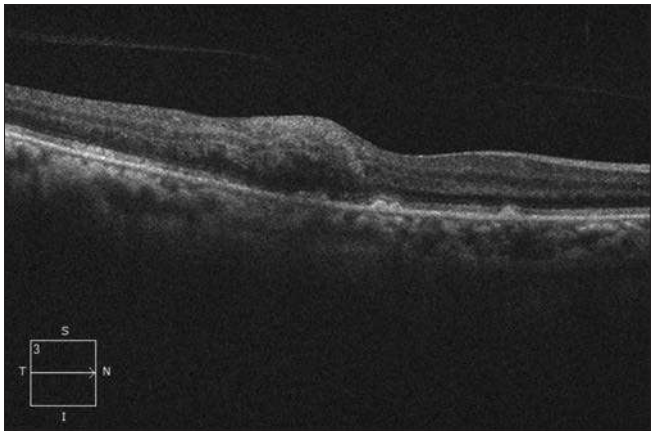


Figure 2: HD raster scan through macula showing loss of retinal layer

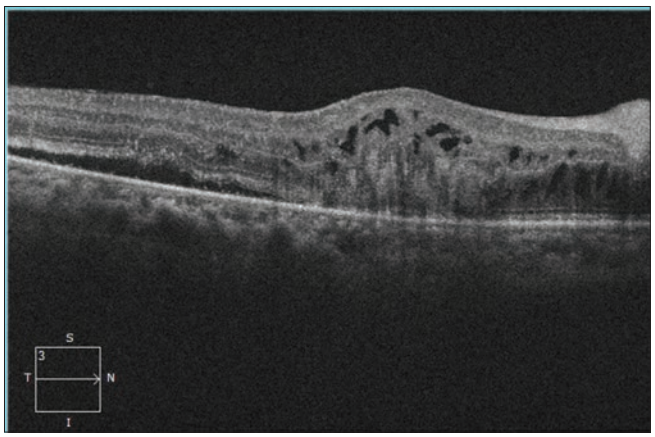


Figure 3: HD raster scan through macula showing prominent middle-limiting membrane sign (a hyperreflective line present at the outer border of inner nuclear layer)

Statistical analysis

The continuous data (CFT) was analyzed using unpaired *t*-test. The categorical data loss of inner retinal layer, loss of foveal IS/OS junction, and p-MLM sign which were compared between two groups was analyzed using Fisher's exact test with GraphPad Prism 9 software (GraphPad software, San Diego, California USA). $P < 0.05$ was considered statistically significant.

OBSERVATION AND RESULTS

A total of 31 eyes of 30 patients having RVO involving macula were evaluated. Out of 30 patients, 18 were males and 12 were females. The mean age was 59.56 ± 8.16 years in the present study. Most of the patients (19) had BCVA ranging from 6/60 to 6/18.

In this study, we divided all studied eyes into two groups on the basis of FFA, Group A and Group B. Eyes which had macular ischemia included in Group A and those with no macular ischemia in Group B. Out of 31 eyes, 17 eyes (54.84%) with macular ischemia [Figure 4] were included in Group A. The remaining 14 (45.16%) eyes had no macular ischemia [Figure 5] and hence included in Group B.

The mean CFT was thinner in the macular ischemia group (432.71 ± 172.30) as compared to the group without macular ischemia (564.57 ± 151.16) and the difference between the two groups was statistically significant ($P < 0.05$) [Table 1].

In this study, we found that the loss of inner retinal layer and loss of foveal IS/OS junction was more commonly associated with the macular ischemia group and this difference was statistically significant $P = 0.0245$ and 0.0292, respectively [Table 2]. We did not find any significant relationship between p-MLM sign and macular ischemia.

DISCUSSION

RVO is the most common vascular cause of unilateral visual impairment. The common causes of visual loss in RVO are macular edema, macular ischemia, and hemorrhage. Macular ischemia is evaluated by FFA which is the conventional method, whereas SD-OCT is a noninvasive technique used for the quantitative analysis of CFT. HD raster macular scan is also performed for qualitative assessment of retinal layers.

In this study, the average CFT was thinner in the macular ischemia group (432.71 μm) than without the macular ischemia group (564.57 ± 151.16; $P = 0.033$). It appeared that thinner CFT in macular ischemia observed in our study may be the result of atrophic changes in the retina due to macular ischemia. Similarly, thinner CFT was observed in the macular ischemia group in the study done by Lima *et al*.[5] The study done by Browning *et al*.[6] noted that the central subfield mean thickness was thinner in severe ischemia but the difference was not statistically significant. In contrast, Murakami *et al*.[7] observed thicker central point thickness in the nonperfused macula group.

In our study, we observed that loss of inner retinal layer ($P = 0.024$) and loss of foveal IS/OS junction ($P = 0.029$) were more commonly associated with ischemic macula. The study done by Lima *et al*.[5] also observed that loss of inner retinal layer at the time of baseline evaluation was more frequently associated with macular ischemia and the difference was statistically significant ($P = 0.03$) but they did not find statistically significant difference between loss of foveal IS/OS junction at the time of baseline evaluation in macular ischemia and without macular ischemia groups ($P = 0.89$).

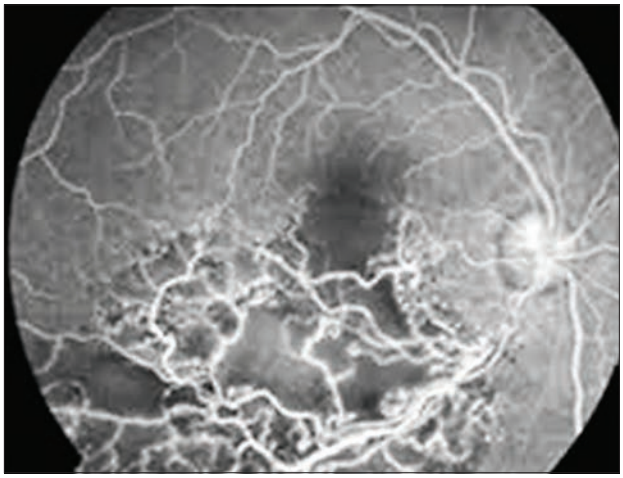


Figure 4: Fluorescein angiography image of a 50-year-old female showing irregular and enlarged foveal avascular zone represents macular ischemia

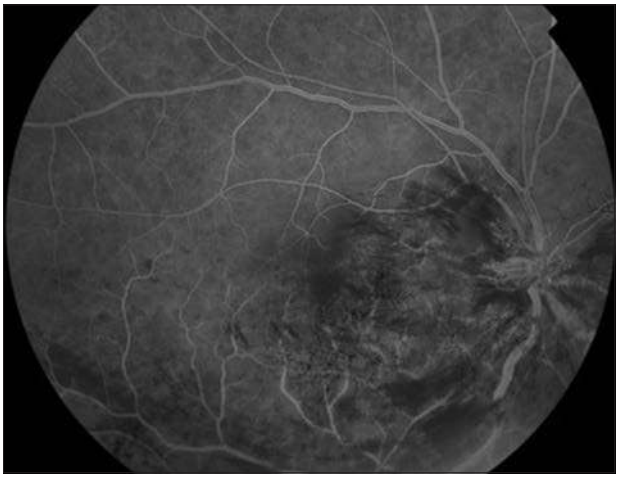


Figure 5: Fluorescein angiography image of 52-year-old male showing regular and <1000 μm foveal avascular zone represents no macular ischemia

Table 1: Central foveal thickness variation between study groups

Central foveal thickness	Group A (with macular ischemia)	Group B (without macular ischemia)	*P*
CFT (μm) mean±SD	432.71±172.30	564.57±151.16	0.033

CFT: Central foveal thickness, SD: Standard deviation

Table 2: Spectral-domain optical coherence tomography findings in the study groups

SD-OCT findings	Group A (with macular ischemia)	Group B (without macular ischemia)	*P*
Loss of inner retinal layers			
Present	10	2	0.0245
Absent	7	12	
Loss of foveal IS/OS junction			
Present	11	3	0.0292
Absent	7	11	
p-MLM sign			
Present	5	3	0.698
Absent	12	11	

SD-OCT – Spectral-domain optical coherence tomography, p-MLM – Prominent middle-limiting membrane, IS – Inner segment, OS – Outer segment

We also assessed p-MLM sign for macular ischemia and could not establish any significant association between macular ischemia and p-MLM sign. Similarly, no significant association of macular ischemia with p-MLM sign in acute central RVO was observed in the study done by Browning *et al*.[6] In contrast, Ko *et al*.[8] suggested a significant association between macular ischemia and p-MLM sign in acute central RVO patients.

Small sample size, interobserver variations in the assessment of macular ischemia, inability in determining macular ischemia by FFA in hazy media and in acute cases presenting with massive intraretinal hemorrhage and during the acute stage, as the retinal morphology is impaired due to scattering effect produced by intraretinal fluid, determination of retinal morphology by SD-OCT scan can be misleading. These are some limitations of our study.

CONCLUSION

From this study, we conclude that SD-OCT parameters such as CFT, loss of inner retinal layer, and loss of foveal IS/OS junction were observed to predict macular ischemia to some extent whereas no association was observed between p-MLM sign with macular ischemia. There are controversies between different studies, so more studies are required for further evaluation of these findings.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Mitchell P, Smith W, Chang A. Prevalence and associations of retinal vein occlusion in Australia. The blue mountains eye study. Arch Ophthalmol 1996;114:1243-7.
2. Klein R, Klein BE, Moss SE, Meuer SM. The epidemiology of retinal vein occlusion: The beaver dam eye study. Trans Am Ophthalmol Soc 2000;98:133-41.
3. Rogers S, McIntosh RL, Cheung N, Lim L, Wang JJ, Mitchell P, *et al*. The prevalence of retinal vein occlusion: Pooled data from population studies from the united states, Europe, Asia, and Australia. Ophthalmology 2010;117:313-9.e1.
4. Chung EJ, Roh MI, Kwon OW, Koh HJ. Effects of macular ischemia on the outcome of intravitreal bevacizumab therapy for diabetic macular edema. Retina 2008;28:957-63.
5. Lima VC, Yeung L, Castro LC, Landa G, Rosen RB. Correlation between spectral domain optical coherence tomography findings and visual outcomes in central retinal vein occlusion. Clin Ophthalmol 2011;5:299-305.
6. Browning DJ, Punjabi OS, Lee C. Assessment of ischemia in acute central retinal vein occlusion from inner retinal reflectivity on spectral domain optical coherence tomography. Clin Ophthalmol 2017;11:71-9.
7. Murakami T, Tsujikawa A, Miyamoto K, Sakamoto A, Ota M, Ogino K, *et al*. Relationship between perifoveal capillaries and pathomorphology in macular oedema associated with branch retinal vein occlusion. Eye (Lond) 2012;26:771-80.
8. Ko J, Kwon OW, Byeon SH. Optical coherence tomography predicts visual outcome in acute central retinal vein occlusion. Retina 2014;34:1132-41.

Case Report

Malignant glaucoma: A therapeutic challenge

ABSTRACT

Malignant glaucoma is a rare condition characterized by an acute rise of intraocular pressure rise with a very shallow anterior chamber, generally following anterior segment surgery. The mechanism leading to malignant glaucoma is that in an anatomically predisposed eye, the anterior rotation of the ciliary body induces misdirection of aqueous flow into or behind the vitreous body, increasing vitreous volume, resulting in anterior displacement of the iris–lens diaphragm, axial and peripheral anterior chamber flattening, and secondary angle closure. The aim of this article is to report a case of malignant glaucoma to discuss about the risk factors involved and therapeutic approaches that are useful in managing such cases.

Keywords: Anterior hyaloidotomy, malignant glaucoma, ultrasound biomicroscopy

INTRODUCTION

Von Graefe in 1869 first described malignant glaucoma. It is a rare condition characterized by an acute rise of intraocular pressure (IOP) rise with a very shallow anterior chamber, generally following anterior segment surgery.

The mechanism leading to malignant glaucoma is poorly understood. The most accepted theory suggests that in an anatomically predisposed eye, the anterior rotation of the ciliary body induces misdirection of aqueous flow into or behind the vitreous body, increasing vitreous volume, resulting in anterior displacement of the iris–lens diaphragm, axial and peripheral anterior chamber flattening, and secondary angle closure.[1,2] The aim of this article is to report a case of malignant glaucoma to discuss about the risk factors involved and therapeutic approaches that are useful in managing such cases.

CASE REPORT

A 52-year-old female, who is a known hypertensive, was referred as having high IOP in the right eye (RE) in spite of maximum medical therapy and a patent peripheral iridectomy. She had history and medical records suggestive of undergoing small incision cataract surgery with intraocular lens (IOL) implantation in RE 10 days back.

On examination, her best-corrected visual acuity was 2/60 in the RE and 6/12 in the left eye (LE). The anterior segment examination in the RE showed hazy cornea with microcystic edema, anterior chamber shallow both centrally and peripherally with iridocorneal touch, dilated and fixed pupil, and IOL in the sulcus with an intact posterior capsule centrally. There were two patent laser peripheral iridectomies at 10'o clock and 2'o clock positions [Figure 1]. She was on tablet acetazolamide 250 mg twice daily, syrup glycerol 30 ml twice daily, topical prednisolone acetate eye drops 1% hourly, and combination of brimonidine 0.2% with timolol 0.5% eye drops. IOP with Goldmann applanation tonometer (GAT) showed

A. Anuradha, M. Vidhya Devi, Rose Mary George, N. Manoj Kumar, Priyam Gupta

Department of Glaucoma, Minto Ophthalmic Hospital, Regional Institute of Ophthalmology, Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India

Address for correspondence: Dr. Rose Mary George, Paikada House, Vazhakulam P.O, Ernakulam - 686 670, Kerala, India.
E-mail: go2roseg@yahoo.com

Submitted: 07-Dec-2020 **Revised:** 02-Jan-2021
Accepted: 09-Mar-2021 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	Quick Response Code
DOI: 10.4103/kjo.kjo_198_20	

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Anuradha A, Devi MV, George RM, Kumar NM, Gupta P. Malignant glaucoma: A therapeutic challenge. Kerala J Ophthalmol 2023;35:198-200.

32 mmHg in spite of all anti-inflammatory and antiglaucoma and medications both topically and systemically. Gonioscopy in the RE showed G0 (closed angles) in all quadrants. Her fundus examination showed a disc with a cup-to-disc ratio of 0.4, pink and healthy neuroretinal rim (NRR), and no retinal nerve fiber layer (RNFL) defects or peripapillary atrophy; macula was hazy with a blunted foveal reflex. LE anterior segment examination was unremarkable except for lens showing cataractous changes. IOP was 8 mmHg with GAT and gonioscopy showed scleral spur (open angle) in all quadrants. Dilated fundus examination showed disc with cup to disc ratio 0.3 and macula was healthy with foveal reflex present. Ultrasound biomicroscopy of the RE showed shallow anterior chamber with iris plastered onto the cornea and anterior rotation and edema of ciliary body [Figure 2].

The patient was diagnosed as RE malignant glaucoma. Nd:YAG laser anterior hyaloidotomy with capsulotomy was done centrally and peripherally with a power of 1.6 mJ on postoperative day 12, which showed aqueous currents in the anterior chamber [Figure 3]. Anterior chamber was deepened slightly, but IOP remained 30 mmHg in the RE.

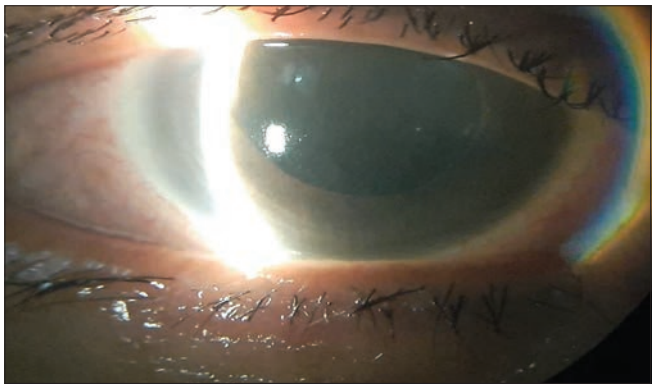


Figure 1: Anterior segment showing hazy cornea with iridocorneal touch and patent peripheral iridectomies

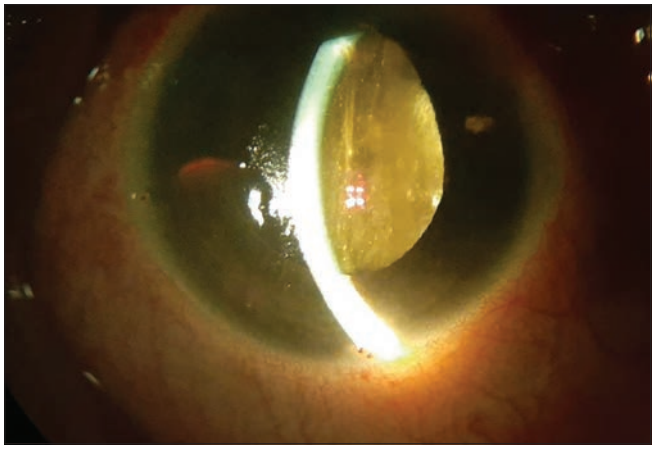


Figure 3: Anterior segment posthyaloidotomy showing aqueous currents and slightly deepened anterior chamber

Since IOP remained high, repeated Nd: YAG laser hyaloidotomy was done on the 14th postoperative day, but IOP remained 30 mmHg in RE in spite of all treatments. Hence on 15th postoperative day, the patient went ahead with vitreous tapping. Preoperative peribulbar anesthesia was given and under aseptic precautions vitreous tapping was done superotemporally and superonasally; about 3.5 mm behind the limbus with a 27G needle. These sites were selected as it was easily accessible and superiorly, there was a sclerocorneal wound post cataract surgery. 0.2ml was aspirated from both sites and it was sent for biochemical evaluation. It was confirmed to be aqueous humor with protein 0.3 g/dl and sugar 92 mg/dl. Anterior chamber was formed with saline and air bubble. Postvitreous tapping day 1 showed well-formed anterior chamber with air bubble *in situ* and IOP was recorded using GAT which showed 18 mmHg. She was tapered on anti-inflammatory and antiglaucoma medications and vision in RE improved, cornea became clear, and IOP remained 16 mmHg on postoperative vitreous tap day 3, with well-formed anterior chamber [Figure 4].

DISCUSSION

Malignant glaucoma is among the most challenging ophthalmologic problems.[3] This case illustrates some of the

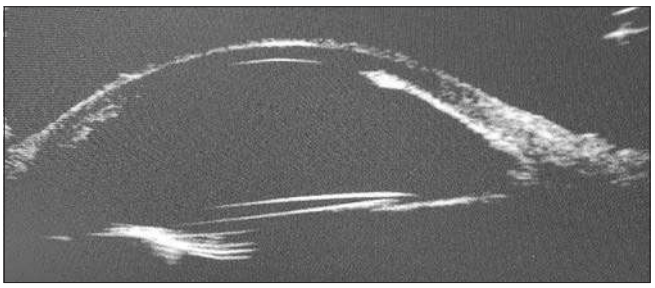


Figure 2: Ultrasound biomicroscopy showing iris plastered onto the cornea with anterior rotation and edema of ciliary body

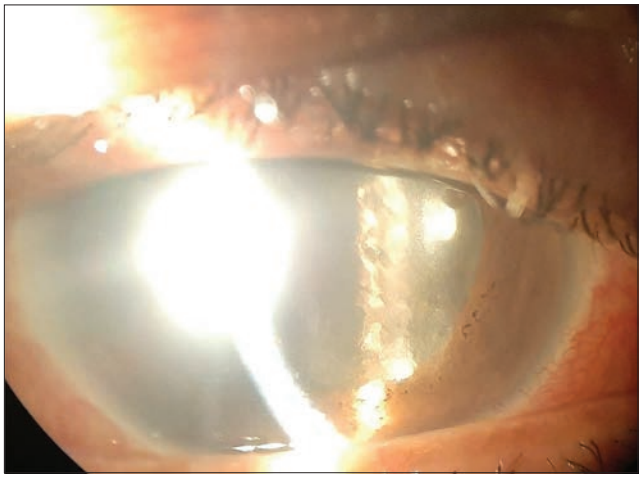


Figure 4: Postoperative vitreous tap day 3 with well-formed anterior chamber

important features and problems that may be encountered during the management of malignant glaucoma. Early recognition and implementation of full medical treatment may enable us not to resort to difficult surgical measures. However, in this case, even though we started on maximum medical treatment early, there were no responses to medical management and had to go ahead with surgical management.

Initial medical therapy is directed at lowering IOP with aqueous suppressants, shrinking the vitreous with hyperosmotic agents, and attempting posterior displacement of the lens–iris diaphragm with a strong cycloplegic such as atropine. A laser iridotomy must be performed if one is not present or if patency of a previous iridotomy cannot be established. The effect of medical therapy is often not immediate, but approximately 50% of cases will be relieved within 5 days. In this case, even with a patent laser iridotomy and maximum medical therapy for 10 days postcataract surgery, the patient was not responding.

Surgical intervention may take the form of laser or involve more invasive surgical procedures. In aphakic or pseudophakic eyes, the Nd: YAG laser may be used to perform posterior capsulotomy/hyaloidotomy. It will only be effective if a direct communication between the vitreous cavity and anterior chamber can be established. It has also been suggested that the use of large optic (7 mm) posterior chamber lens implants may increase the risk of developing malignant glaucoma postoperatively and may also present an obstacle to successful hyaloidotomy as they may prevent adequate flow of aqueous from the vitreous into the anterior chamber.[4] One way of improving the likely outcome of Nd: YAG laser therapy is to make the capsular opening through a dialing hole where present, thus allowing a direct passage of aqueous between vitreous cavity and anterior chamber.[5]

In 1968 Chandler described the technique of vitreous aspiration through an 18 gauge needle via an incision 4 mm behind the limbus in conjunction with anterior chamber reformation with saline.[6] This and similar techniques have remained in common use and with successful outcome in many eyes.[7] However, this technique depends on the surgeon passing a needle 12 mm into the vitreous cavity in an almost blind manner and is not without its hazards. Due this this and because of improved microsurgical equipment and techniques, more recently pars plana vitrectomy, with or without lensectomy, has been advocated for the surgical management of malignant glaucoma.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Debrouwere V, Stalmans P, Van Calster J, Spileers W, Zeyen T, Stalmans I. Outcomes of different management options for malignant glaucoma: A retrospective study. Graefes Arch Clin Exp Ophthalmol 2012;250:131-41.
2. Dave P, Senthil S, Rao HL, Garudadri CS. Treatment outcomes in malignant glaucoma. Ophthalmology 2013;120:984-90.
3. Shahid H, Salmon JF. Malignant glaucoma: A review of the modern literature. J Ophthalmol 2012;2012:852659. Epub 2012 Mar 27. PMID: 22545204; PMCID: PMC3321564.
4. Melasmed S, Ashkenazi I, Blumenthal M. Nd-YAG laser hyaloidotomy for malignant glaucoma following one-piece 7mm intraocular lens implantation. Br J Ophthalmol 1991;75:501-3.
5. Risco JM, Tomey KF, Perkins TW. Laser capsulotomy through intraocular lens positioning holes in anterior aqueous misdirection. Case report. Arch Ophthalmol 1989;107:1569.
6. Chandler PA, Simmons RJ, Grant WM. Malignant glaucoma. Medical and surgical treatment. Am J Ophthalmol 1968;66:495-502.
7. Simmons RJ, Thomas JV, Yaqub M. Malignant glaucoma. In: Ritch R, Shields MB & Krupin T (eds). The glaucomas. St Louis: CV Mosby 1989;1251-63.

Case Report

Hyperacute spontaneous closure of a traumatic macular tear in a middle-aged female

ABSTRACT

We report a case of a keyhole-shaped macular tear following blunt trauma and its spontaneous closure within 2 weeks in a middle-aged female. A 45-year-old female presented with unilateral acute diminution of vision following blunt trauma. Clinical examination revealed an atypical keyhole-shaped macular tear. Spontaneous closure of the tear was noted at the next review at 2 weeks. Most cases of spontaneous closure reported in the literature are in younger patients and after 1 month of trauma. Our case is unique because of the relatively older age of the patient, early spontaneous closure, and atypical configuration of tear.

Keywords: Macular hole, macular tear, spontaneous closure, traumatic macular hole

INTRODUCTION

Blunt trauma can cause several posterior segment manifestations such as vitreous, preretinal, subretinal and intraretinal hemorrhages, commotio retinae, retinal tears and dialysis, retinal detachment, choroidal rupture, and macular holes. There have been reports of macular tears with an unusual horseshoe-shaped configuration after trauma in literature.[1-3] We report a similar case of a keyhole-shaped macular tear in a middle-aged female and spontaneous closure of the tear in 2 weeks.

CASE REPORT

A 45-year-old female patient presented to us 1 day after sustaining blunt trauma to her left eye during an alleged assault and injury with a closed fist. Her previous medical and ocular history was unremarkable. The best-corrected visual acuity (BCVA) on the day of examination was counting fingers at 2 meters. Anterior segment examination showed traumatic iritis which was treated with topical steroids and cycloplegics. Fundoscopy showed a full-thickness defect in the macula of keyhole configuration with surrounding subretinal fluid and intraretinal hemorrhages [Figure 1a]. Spectral-domain optical coherence tomography (SD-OCT) was performed which confirmed the findings of fundoscopy. SD-OCT showed a full-thickness defect in the neurosensory retina with surrounding subretinal fluid. Wrinkling of inner retinal layers was also noticed [Figure 1c]. Posterior vitreous detachment was not detected clinically or by SD-OCT. Chances of spontaneous closure were explained to the patient. She was reviewed at 2 weeks. The BCVA improved to 20/120 during this visit. Fundus examination showed closure of the macular tear with pigmentary changes [Figure 1b]. SD-OCT showed closure of the tear with foveal atrophy and photoreceptor loss [Figure 1d].

DISCUSSION

Traumatic macular hole (TMH) is a common complication of ocular blunt trauma. It can occur immediately following trauma

Syed Mohideen Abdul Khadar, Jahnara Jaffar

Department of Retina and Vitreous, Aravind Eye Hospital and Post Graduate Institute of Ophthalmology, Tirunelveli, Tamil Nadu, India

Address for correspondence: Dr. Jahnara Jaffar, Aravind Eye Hospital and Post Graduate Institute of Ophthalmology, Tirunelveli, Tamil Nadu, India.
E-mail: jahnarajunaid@gmail.com

Submitted: 19-Jun-2021 **Revised:** 28-Jun-2021 **Accepted:** 06-Jul-2021 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	Quick Response Code
DOI: 10.4103/kjo.kjo_146_21	

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Khadar SM, Jaffar J. Hyperacute spontaneous closure of a traumatic macular tear in a middle-aged female. Kerala J Ophthalmol 2023;35:201-2.

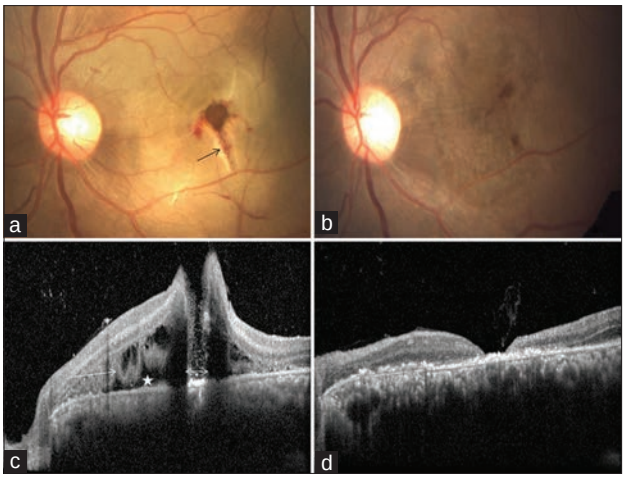


Figure 1: (a) Fundus photo of left eye taken on first visit showing key-hole shaped macular tear (Black arrow). (b) Fundus Photo at 2 weeks review showing spontaneously closed macular tear with retinal pigment epithelium degeneration. (c) Spectral domain optical coherence tomography image of left eye taken on first visit, showing full thickness defect in neurosensory retina (double headed arrow). Note the subretinal fluid (white star) and wrinkling of inner retinal layers (white arrow) (d) Spectral domain optical coherence tomography at 2 weeks showing closure of the defect with foveal atrophy and loss of photoreceptor layer

due to concussive damage and retinal dehiscence at the macula and result in immediate visual loss. Delayed hole formation can occur due to changes in vitreo-retinal interface induced by trauma. In such instances, the visual loss may not be apparent immediately following the trauma.[4] The macular tear in our case is different from a typical macular hole due to its unusual shape and the presence of irregular edges. Presumably, the tear developed at the same time of injury. Karaca *et al*. has reported a similar case of horseshoe-shaped traumatic macular tear and its spontaneous closure within 1 month in a 21-year-old male patient.[2] They hypothesized that if the vitreous attachments surrounding the macula are not equal in all directions, the sudden traction exerted on the macula may result in a tear and not a hole. Similar mechanism may exist in our case as well. However, in contrast to their case, our case had significant visual improvement after spontaneous closure, even though SD-OCT showed foveal atrophy and photoreceptor loss.

Spontaneous closure of TMH is common, but rarely occurs after the age of 30.[5,6] In young patients, there is firm vitreofoveal adhesion and an intact vitreous gel. The sudden impact of the trauma exerts traction at the sites of vitreofoveal adhesions causing macular tear/hole formation. However, this traction is transient. The intact vitreous gel continues to tamponade the TMH, which may help in spontaneous closure. Spontaneous closure within 2 weeks is also rarely reported in the literature.[7] There is a paucity of histological evidence regarding the mechanism of spontaneous closure in TMHs. The most accepted theory is that of glial and retinal pigment epithelial proliferation to fill up the defect. Age <30-year, the absence of posterior vitreous detachment and small size of TMH are associated with spontaneous closure.[8] Our case is distinct because of the relatively older age of the patient and closure of the tear within 2 weeks.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Mito T, Joko T, Shiraishi A. Development of traumatic bilateral horseshoe-shaped macular tear without vitreous traction: Case report. Indian J Ophthalmol 2020;68:936-8.
2. Karaca U, Durukan HA, Mumcuoglu T, Erdurman C, Hurmeric V. An unusual complication of blunt ocular trauma: A horseshoe-shaped macular tear with spontaneous closure. Indian J Ophthalmol 2014;62:501-3.
3. Goel N, Sharma R, Mandal M, Choudhry RM. Posttraumatic horseshoe-shaped macular tear. Indian J Ophthalmol 2014;62:1103-4.
4. Yamashita T, Uemara A, Uchino E, Doi N, Ohba N. Spontaneous closure of traumatic macular hole. Am J Ophthalmol 2002;133:230-5.
5. Grassi P, Salicone A. Delayed spontaneous closure of traumatic macular hole in a 66-year-old patient-role of optical coherence tomography follow-up. GMS Ophthalmol Cases 2020;10:Doc41.
6. Nasr MB, Symeonidis C, Tsinopoulos I, Androudi S, Rotsos T, Dimitrakos SA. Spontaneous traumatic macular hole closure in a 50-year-old woman: A case report. J Med Case Rep 2011;5:290.
7. Misra DK, Barman M, Deori N, Upadhyay A. Hyperacute spontaneous closure of a traumatic macular hole in a colobomatous eye. Am J Ophthalmol Case Rep 2019;15:100504.
8. Miller JB, Yonekawa Y, Eliott D, Kim IK, Kim LA, Loewenstein JI, *et al*. Long-term Follow-up and Outcomes in Traumatic Macular Holes. Am J Ophthalmol 2015;160:1255-8.e1.

Case Report

Corneal component surgery: Expanding the indications

ABSTRACT

Despite immense progress in eye banking and corneal transplantation in the past few years in India, we still have a long way to go. The acute shortage of good-quality donor corneal tissues calls for innovative methods to ensure optimum utilization of the available resources including corneal tissues. The recent advances in lamellar surgery techniques have enabled use of one donor corneal tissue in multiple recipients. The authors discuss their experience of using one cornea in three patients with different corneal pathologies. Component corneal surgery is bound to play a key role in combating corneal blindness in India.

Keywords: Blindness, component, corneal, donor

INTRODUCTION

Corneal transplant surgery is considered as the most successful of all organ transplants because of the unique property of avascularity of the cornea – giving it a state of immune privilege. Over the last couple of decades, there has been a paradigm shift from the full-thickness penetrating keratoplasty (PKP) to lamellar keratoplasty (KP) which offers advantages of preservation of ocular surface and endothelial cells, avoids suture-related complications, and also provides better ocular integrity.

Components that can be used for transplant are epithelium, epithelial stem cells, Bowman layer, stroma, and endothelium. Recent emphasis has been on minimum surgical trauma, specialized lamellar KP techniques, selective excision of diseased corneal tissue, and replacement by healthy donor corneal tissue. Utilization of one cornea for multiple recipients has immense value in developing countries with a paucity of corneal donor tissues. Lamellar KP also offers unique opportunity to use various components of cornea individually in different patients, leading to the concept of component corneal surgery. It was first conceptualized by Shimmura in 2004.[1] Subsequently, various innovative uses have been reported in literature. Component surgeries of the cornea have several advantages that include decreased the risk of graft rejection and avoidance of complications associated with open-sky procedures.[2,3] Further, these surgical techniques entail the utilization of one donor cornea for multiple recipients, which have a value in developing countries such as ours where there is a paucity of good-quality donor corneal tissue. Herein, we share our experience in expanding these indications.

CASE REPORTS

A good-quality donor cornea with endothelial count of 2717/mm^2 was retrieved from a 49-year-old male donor within 3 h of death, who had died of cardiac arrest and stored in optisol. The donor blood sample tested negative for human immunodeficiency virus, hepatitis B surface antigen, hepatitis

Nimisha Nagpal, Pawan Prasher[1]

Department of Ophthalmology, Sri Guru Ram Das Institute of Medical Sciences and Research, [1]Department of Ophthalmology, Amritsar Eye Hospital, GNDU Shopping Complex, GT Road, Amritsar, Punjab, India

Address for correspondence: Dr. Pawan Prasher, Professor, Department of Ophthalmology, Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, Punjab, India.
E-mail: pawanprasher@yahoo.com

Submitted: 01-Feb-2021 **Revised:** 30-Mar-2021
Accepted: 17-Jul-2021 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	Quick Response Code
DOI: 10.4103/kjo.kjo_32_21	

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Nagpal N, Prasher P. Corneal component surgery: Expanding the indications. Kerala J Ophthalmol 2023;35:203-6.

B core antigen, and syphilis antigen. Donor cornea was precut by the eyebank and subsequently trephined, providing the donor tissue in three parts:

1. The anterior lamellar disc, consisting of partial-thickness corneal stromal tissue
2. The posterior lamellar disc, consisting of corneal stroma, descemet membrane, and endothelium
3. The peripheral corneoscleral rim, which harbors the limbal stem cells.

Case 1

DSEK

A 40-year-old male complained of diminution of vision right eye for the past 6 months. He had undergone PKP 1 year back with good postoperative vision for first few months, but there was gradual deterioration afterward. His best-corrected visual acuity (BCVA) at presentation was 20/100.

Slit-lamp evaluation showed stromal haze which was illustrated on anterior segment imaging [Figure 1a]. The surgical technique planned for the patient consisted of stripping the Descemet membrane and endothelium from the recipient's central cornea and placing a donor graft. Donor graft was retrieved and transplanted an 8.0-mm disc of donor endothelium and posterior stroma was transplanted through a 5 mm temporal corneoscleral incision. Postoperative day 1, BCVA was 20/40 (P) with graft in place with air bubble present and anterior chamber formed [Figure 1b]. On postoperative 3 months visit, the graft was intact and clear with BCVA 20/20 (P) [Figure 1c].

Case 2

Anterior lamellar graft

A 50-year-old female was referred to our outpatient department for the management of a nonhealing corneal ulcer in her left eye involving anterior two-third of the stroma. She was previously treated with topical and systemic antifungals with regular debridement of the infiltrate which lead to resolution of infiltrate but marked thinning of corneal stroma, leading to descemetocele with impending perforation [Figure 2a]. Her preoperative BCVA was hand motions close to the face. A 3 mm patch graft was fashioned from the anterior lamellar disc of the donor cornea and sutured over the descematocoele to provide tectonic support. The postoperative treatment included a combination of natamycin 5% eye drops every 2 h, 0.5% moxifloxacin hydrochloride eye drops 3 times daily, and preservative-free tear substitutes every 4 h. On postoperative day 1, her graft was in place with sutures intact [Figure 2b]. Her postoperative BCVA on 3 month visit was 20/60 in her left eye [Figure 2c].

Case 3

Corneoscleral patch graft

Partial-thickness corneoscleral lenticule was harvested from the peripheral corneoscleral rim of the donor cornea and transplanted into the right eye of a 45-year-old male who had been diagnosed with perforated crescent-shaped corneal ulcer (Peripheral Ulcerative Keratitis) on the nasal limbus with BCVA as 20/200. A perforation measuring 3.5 mm × 2.5 mm in diameter was seen at limbus at 3 o'clock position with iris prolapse [Figure 3a].

The corneoscleral rim of the donor button was trimmed to prepare an appropriately sized corneal scleral tectonic graft. The graft was sutured to the host bed after doing a conjunctival resection and freshening of the margins. On postoperative day 1 [Figure 3b], the graft was in place and interrupted sutures were intact with BCVA as 20/100, whereas his BCVA improved to 20/60 on postoperative day 21 [Figure 3c].

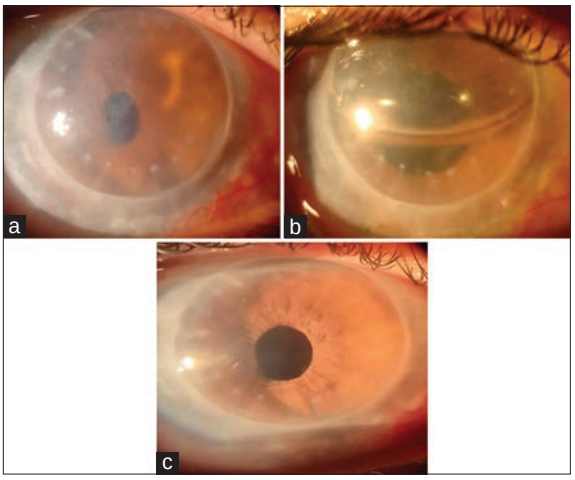


Figure 1: Slit-lamp illustrating (a) increased corneal endothelial odema leading to graft failure in diffuse illumination preoperatively (b) postoperative day 1 and (c) postostoperative 3 months with graft intact

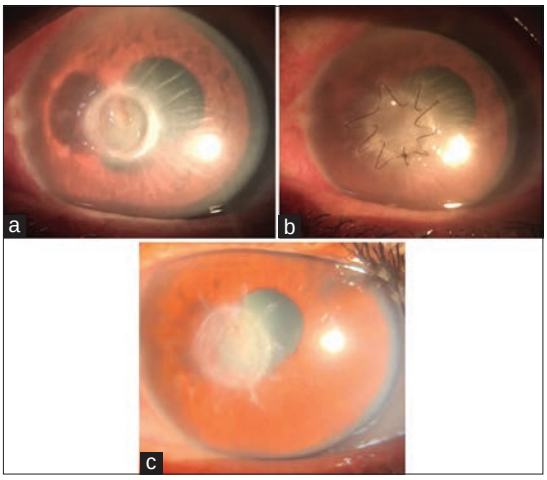


Figure 2: Slit-lamp picture showing (a) descemetocele with impending perforation in the left eye preoperatively (b) postoperative day 1 with 1 continuous sutures intact (c) postoperative at 3 months after suture removal

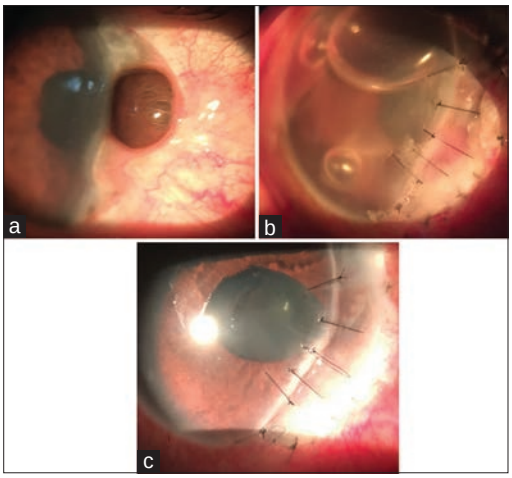


Figure 3: Slit-lamp biomicroscopy picture illustrating (a) perforated crescent-shaped corneal ulcer on the nasal limbus postperipheral ulcerative keratitis (b) postoperative day 1 and (c) postoperative day 21 with interrupted sutures intact

The postoperative treatment included a combination of 1% prednisolone acetate eye drops every 4 h, 0.5% moxifloxacin hydrochloride eye drops 3 times daily, 2% cyclosporine eye drops 4 times daily, and preservative-free tear substitutes every 4 h along with rheumatologist consultation. A bandage contact lens was put into the operated eye.

DISCUSSION

There are currently an estimated 15 million blind people in India out of which 6.8 million of these suffer from corneal blindness. Of these at least 3 million can benefit by corneal transplantation.[3]

In developing countries such as India, there is a marked shortage of good-quality corneal tissue. In the setting of an annual requirement of 300,000 corneas, only 15,000 are available out of which almost half are unsuitable for transplantation. The need for donor corneas per year in India is at least 20 times the current procurement.[4] There is a huge gap between demand and supply. To address this gap, customized component corneal transplantation appears an exciting proposition. It seems to have the potential to reduce the demand by a 3-fold magnitude.

The concept of component surgery of cornea was pioneered by Shimmura in 2004.[1] Subsequently, Vajpayee *et al*.[5] carried forward this concept of using one donor cornea for three recipients. Encouraged by these results, Sharma *et al*.[6] and Heindl *et al*.[7] demonstrated that a single donor cornea could be successfully transplanted using anterior lamellar and posterior Descemet membrane along with the remaining corneal stromain in different patients and in their series, they reported good visual outcomes for both the recipients. A similar case with multiple recipients was discussed by Sati *et al*.[8] providing us guidance towards a better outcome, but the recipient conditions were different. Most recently, Maharana *et al*.,[9] in a review article laid emphasis on appropriate utilization of all components of donor corneal button illustrating different techniques which could be used for the same.

We can optimally utilize the corneal donor button for different levels of pathology. Anterior lamellar button for anterior epithelial or stromal and posterior button for endothelial KP. Peripheral healthy donor corneal tissue can also be carefully salvaged and used as small patch grafts or banana grafts for peripheral ulcerative keratitis/Mooren's ulcer, limbal stem cell transplantation, or covering for glaucoma tube shunts. An added advantage of performing split cornea transplantation is the reduction in the total cost of the procedures.

A policy of multiple use of single donor tissue can be implemented more successfully if a suitable pool of patients, who are waiting for KP, is organized. There is an urgent need for awareness among eye care professionals regarding early referral of patients requiring Descemet stripping automated endothelial keratoplasty. It is a known fact that with time, stromal scarring develops in patients with bullous keratopathy, making them unsuitable for a posterior lamellar KP. Also, a corneal ulcer worsening/not responding to treatment, impending perforation, and descemetocele must be referred to a facility for PKP without delay.

Concerns for the surgeon are a large learning curve for both anterior and posterior lamellar keratoplasties. Furthermore, the availability of a spare cornea should be ensured before proceeding for split corneal transplantation as in case of inadvertent corneal perforation during deep anterior lamellar KP conversion to PKP may be required. This case report highlights the successful outcome of a customized component corneal transplantation that is, using one corneoscleral button for three recipients. This innovative concept is a small step towards finding solutions for an everlasting shortage of good-quality donor tissue in developing countries.

CONCLUSIONS

Rapid progress is being made in the fields of anterior lamellar and endothelial KP. Besides using anterior and posterior layers of donor cornea for anterior lamellar KP and Descemet's stripping endothelial KP, it is a novel concept to also use the anterior lamella and corneoscleral rim for a patch graft. Trend toward more selective replacement of diseased corneal tissue layer may continue to decrease indications for full-thickness PKP in future.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Shimmura S. Component surgery of the cornea. Cornea 2004;23:S31-5.
2. Tan DT, Mehta JS. Future directions in lamellar corneal transplantation. Cornea 2007;26:S21-8.
3. Patel AK, Scorcia V, Kadyan A, Lapenna L, Ponzin D, Busin M. Microkeratome-assisted superficial anterior lamellar keratoplasty for anterior stromal corneal opacities after penetrating keratoplasty. Cornea 2012;31:101-5.
4. Rajshekhar Vemparala, Promila Gupta. National Programme for Control of Blindness (NPCB) in the 12th Five year plan: An Overview. DJO 2017;27:290-2.
5. Vajpayee RB, Sharma N, Jhanji V, Titiyal JS, Tandon R. One donor cornea for 3 recipients: a new concept for corneal transplantation surgery. Arch Ophthalmol 2007;125:552-4.
6. Sharma N, Agarwal P, Titiyal JS, Kumar C, Sinha R, Vajpayee RB. Optimal use of donor corneal tissue: one cornea for two recipients. Cornea 2011;30:1140-4.
7. Heindl LM, Riss S, Laaser K, Bachmann BO, Kruse FE, Cursiefen C, *et al.* Split cornea transplantation for 2 recipients–Review of the first 100 consecutive patients. Am J Ophthalmol 2011;152:523-32.
8. Sati A, Shankar S, Jha A, Gurunadh VS. Customised component corneal transplantation: a blessing for three patients. BMJ Case Rep. 2014;2014:bcr 2014205.
9. Maharana PK, Sahay P, Singhal D, Garg I, Titiyal JS, Sharma N. Component corneal surgery: An update. Indian J Ophthalmol 2017;65:658-72.

Case Report

Presumed silicone oil droplets following intravitreal bevacizumab injection

ABSTRACT

A 67-year-old male presented with loss of vision in the right eye of 3-month duration. He was diagnosed as superotemporal branch retinal vein occlusion with macular edema and was treated with 4 monthly intravitreal bevacizumab injections. Following the fourth injection, multiple tiny presumed silicone oil droplets were noted in the vitreous. The patient was asymptomatic, and the oil droplets stayed stable during the follow-up period.

Keywords: Bevacizumab, intravitreal injection, silicone oil

INTRODUCTION

Intravitreal injections are being routinely used in day-to-day retina practice for treating a variety of retinal disorders. Bevacizumab (Avastin; Genentech, Inc.) is being used in the intravitreal route to treat disorders such as diabetic retinopathy, branch retinal vein occlusion, and choroidal neovascular membrane.[1] Although it is not approved by the Food and Drug Administration for intraocular use, it has gained worldwide acceptance because it is a cheaper alternative to its peers available in the market.

Complications following intravitreal injections include vitreous hemorrhage, retinal detachment, traumatic injury to lens, infective and sterile endophthalmitis, intraocular inflammation, and retinal tears. Most of these complications are procedure related. Retained silicone oil droplets following intravitreal injections have been previously reported in the literature.[2-6] We report a case of retained silicone oil droplets in the vitreous following intravitreal bevacizumab for branch retinal vein occlusion.

CASE REPORT

A 67-year-old hypertensive male presented with complaints of gradual onset loss of vision in his right eye (RE) of 3-month duration. He was diagnosed elsewhere with a retinal disorder and was referred to our center. Best-corrected visual acuity in RE was 20/80, N18 and the left eye (LE) was 20/32, N6. Anterior segment examination using slit lamp showed nuclear sclerosis Grade I with early posterior subcapsular cataract in both eyes. Intraocular pressure measured using Goldmann applanation tonometer was 17 and 16 mmHg in RE and LE, respectively. Fundus examination of RE revealed superotemporal branch retinal vein occlusion (STBRVO) and normal fundus in LE. Gross cystoid macular edema with neurosensory detachment was noted on optical coherence tomography in RE. Central retinal thickness was 495 µ and 234 µ in RE and LE, respectively. The patient was advised monthly intravitreal injections of bevacizumab in RE. The patient received 4 monthly doses of intravitreal bevacizumab in his RE. There was a gradual decrease in cystoid macular edema and height of neurosensory detachment with marked improvement of vision following the

Pradeep Kumar Panigrahi, Jasmita Satapathy, Yamijala Neha Srija

Department of Ophthalmology, Institute of Medical Sciences and SUM Hospital, Siksha "O" Anusandhan (Deemed to be) University, Bhubaneswar, Odisha, India

Address for correspondence: Dr. Pradeep Kumar Panigrahi, Department of Ophthalmology, Institute of Medical Sciences and SUM Hospital, Siksha "O" Anusandhan (Deemed to be) University, 8-Kalinga Nagar, Bhubaneswar - 751 003, Odisha, India.
E-mail: doc.pkp25@gmail.com

Submitted: 12-Jan-2021 **Revised:** 20-Jan-2021 **Accepted:** 25-Jan-2021 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	Quick Response Code
DOI: 10.4103/kjo.kjo_9_21	

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Panigrahi PK, Satapathy J, Srija YN. Presumed silicone oil droplets following intravitreal bevacizumab injection. Kerala J Ophthalmol 2023;35:207-9.

injections. When the patient followed up with us 1 month after the fourth injection, best-corrected visual acuity in RE had improved to 20/32, N6 and macular edema had completely resolved. Fundus examination showed resolved STBRVO in RE [Figure 1a]. A closer look with indirect ophthalmoscopy revealed the presence of 3–4 tiny spherical, translucent silicone oil-like droplets in the superior vitreous close to the retinal surface [Figure 1b]. The droplets were freely floating in the vitreous and tended to move superiorly with change in position of the head. There was no evidence of any anterior segment inflammation. Since the oil droplets were not interfering with vision, we decided to closely follow up the patient. The patient was followed up for 6 months. He did not require any further intravitreal injection in RE. At final follow-up, the patient was maintaining a vision of 20/32, N8 in RE and the silicone oil-like droplets were still present in the superior vitreous. There was no change in the size of the droplets at the final visit.

DISCUSSION

We have reported a case of presumed silicone oil droplets following repeated intravitreal injections. These droplets are usually multiple, spherical, translucent and can be easily detected on routine slit-lamp biomicroscopy and indirect ophthalmoscopy. Their appearance is identical to the silicone oil droplets seen in patients undergoing silicone oil tamponade after vitrectomy. Our patient received four doses of intravitreal bevacizumab following which the oil droplets were noted. Standard 1 ml tuberculin syringe and a ½-inch 30G needle were used for all four injections in our case. The oil droplets remained suspended in the vitreous and did not cause any symptoms during follow-up. Retained silicone oil droplets have been reported following intravitreal injections of bevacizumab, ranibizumab, and pegaptanib. Similar to our case, most of the patients had received multiple doses of the agent following which the droplets were noted. Most of the cases were asymptomatic throughout the follow-up period with multiple small oil droplets. Yu *et al*.[4] reported seven cases of silicone oil droplets following intravitreal injection of bevacizumab. All these patients were symptomatic and complained of floaters following the injections. Avery *et al*.[5] have reported large silicone oil droplets following intravitreal bevacizumab injection in 23 patients. Patients frequently noted a circular floater consisting of a dark ring surrounding a bright central area immediately following the treatment.

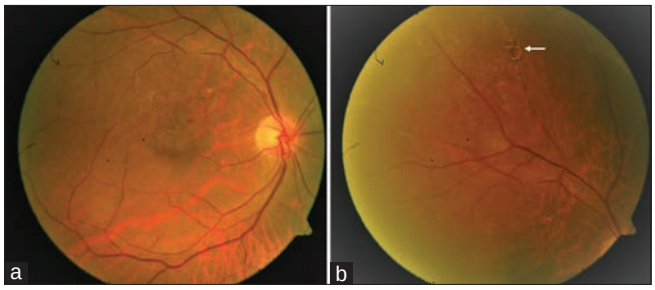


Figure 1: (a) Color fundus photograph of the right eye showing resolved superotemporal branch retinal vein occlusion. (b) Color fundus photograph of the mid-peripheral retina (superior) showing 3–4 presumed silicone oil droplets (white arrow)

The source of this presumed silicone oil is believed to be either the syringe or needle used to deliver the drug. Polydimethylsiloxane is used as a lubricant for the syringe barrel, piston, and needle siliconization of the inner syringe wall and outer plunger surface serve to decrease friction for piston movement and minimize protein absorption to prolong drug stability. Because silicone oil has a relatively low cohesiveness, it may migrate into the syringe and contaminate the drug.[2] Chantela *et al*.[7] have reported the release of silicone oil from disposable syringes during insulin expulsion resulting from mechanical abrasion and flushing actions on the siliconized plastic surfaces of the syringe barrel and plunger. Another source of silicone could be the needle itself, which is also lubricated with silicone oil. It is possible that the eyewall squeezed a small amount of the lubricant off of the needle as it was removed from the eye.

To conclude, retained silicone oil droplets are a rare complication following intravitreal injection. To the best of our knowledge, this is the first such case report on Indian population. Patients are mostly asymptomatic but can complain of symptomatic floaters if the size of the droplets is large. With increasing number of intravitreal injections in retina practice, one should remain vigilant and look for such droplets carefully. Mention of such rare complication in the patient consent form should be considered to prevent future medicolegal hassles. Improved design of the syringes and the use of silicone-free syringes can reduce such complications.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Michels S, Prager F, Bakri SJ, Wachtlin J. Bevacizumab for ophthalmic diseases. Expert Rev Ophthalmol 2007;2:369-78.
2. Kocabora MS, Ozbilen KT, Serefoglu K. Intravitreal silicon oil droplets following pegaptanib injection. Acta ophtalmologica 2010;88:44-5.
3. Freund KB, Laud K, Eandi CM, Spaide RF. Silicone oil droplets following intravitreal injection. Retina 2006;26:701-3.
4. Yu JH, Gallemore E, Kim JK, Patel R, Calderon J, Gallemore RP. Silicone oil droplets following intravitreal bevacizumab injections. Am J Ophthalmol Case Rep 2018;10:142-4.
5. Avery RL, Castellarin AA, Dhoot DS, Pieramici DJ, Nasir MA, Steinle NC, *et al.* Large silicone droplets after intravitreal bevacizumab (Avastin). Retin Cases Brief Rep 2019;13:130-4.
6. Bakri SJ, Ekdawi NS. Intravitreal silicone oil droplets after intravitreal drug injections. Retina 2008;28:996-1001.
7. Chantelau E, Berger M, Böhlken B. Silicone oil released from disposable insulin syringes. Diabetes Care 1986;9:672-3.

Case Report

Frontalis sling in a bilateral ptosis with external ophthalmoplegia and poor bell's phenomenon: A 5-year follow-up

ABSTRACT

Congenital ptosis with ophthalmoplegia is a rare condition. We present a 17-year-old patient with congenital ptosis with severe restriction of ocular movements with poor Bell's phenomenon. He was managed with silicone rod frontalis sling surgery. After 5 years, the sling is intact with no lagophthalmos and exposure keratopathy.

Keywords: Congenital ptosis, frontalis sling, silicone rod

INTRODUCTION

Blepharoptosis or ptosis is a common clinical sign that may affect individuals of all ages. Ptosis is a drooping or inferior displacement of the upper eyelid with associated narrowing of the vertical palpebral fissure. The drooping may be slight or insignificant or severe that it covers the pupil and causes visual disturbance. Ptosis is caused by a dysfunction of the muscles and/or nerves that regulate the elevation of the eyelid. Two separate muscles are involved in the elevation of the eyelid – the levator palpebrae superioris, which is innervated by the superior branch of the III cranial nerve and the superior tarsal muscle (Müller's muscle), which is innervated by the cervical sympathetic system and elevates the posterior portion of the eyelid. Normally, the upper eyelid is positioned 1–2 mm below the upper corneal limbus, and the lower eyelid is placed at the sclerocorneal junction.[1]

Griepentrog *et al*. have estimated that nearly 90% of ptosis was congenital.[2] Only 3% were bilateral, and the left side was consistently more affected (68%) compared to the right. It is a benign condition but causes functional, cosmetic, and psychological problems in children. Prompt surgical correction is needed only for patients at risk for amblyopia with deferred or no surgery possible for patients who are not at risk for amblyopia.[3]

We present a case with congenital ptosis and severe restriction of ocular movements with poor Bells phenomenon. He underwent frontalis sling surgery at the age of 17 years. Even after 5 years, the slings are intact and there is no evidence of lagophthalmos and exposure keratitis.

CASE REPORT

A 17-year-old male presented at the ophthalmology outpatient department of the study institute with complaints of drooping of both upper lids since birth. He had an abnormal head posture with chin elevation. He said his father and grandfather had the same problem and his father did

N. V. Latha, M Vishnupriya

Department of Ophthalmology, Government Medical College, Kannur, Kerala, India

Address for correspondence: Dr. N. V. Latha, Department of Ophthalmology, Government Medical College, Kannur - 670 503, Kerala, India.
E-mail. dr.lathamohanacme@gmail.com

Submitted: 28-Aug-2021 **Revised:** 05-Sep-2021
Accepted: 10-Sep-2021 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	Quick Response Code
DOI: 10.4103/kjo.kjo_187_21	

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Latha NV, Vishnupriya M. Frontalis sling in a bilateral ptosis with external ophthalmoplegia and poor bell's phenomenon: A 5-year follow-up. Kerala J Ophthalmol 2023;35:210-4.

not take any treatment for that. He was referred to a higher center from his hometown where he was advised surgery to correct the ptosis. However, his family could not afford the surgery due to financial constraints, and hence, he came for a consultation to the study institute, which is a public sector teaching institute in North Kerala.

On examination, the boy had severe bilateral ptosis [Figure 1]. The visual acuity was 6/18 in both eyes. The extraocular movements were grossly restricted with inferiorly placed eyeballs. The levator palpebrae superioris function was 3 mm. Bell's phenomenon was very poor. Pupils were 3 mm and reacting normally. Marcus Jaw winking phenomenon was absent. Other cranial nerves, central nervous system, and systemic examination did not reveal any obvious abnormality.

The patient wanted the ptosis to be corrected. The patient and parents were counseled on the various treatment options that were possible at the public sector study institute and the complications associated with the different procedures. They were willing for the ptosis correction without correcting the ocular alignment. Informed consent was obtained from the patient before the surgery.

After adequate preoperative assessment and explaining the risks, frontalis sling surgery was done with silicone rod (AUROSLING) bilaterally under general anesthesia under all aseptic precautions.

The skin was marked meticulously on the right side in a pentagon fashion with methylene blue after proper cleaning and draping. Two stab incisions were marked in the lid 2 mm from the lash line at the junctions of the inner and middle thirds and middle and outer thirds of the upper lid. The medial and lateral brow incisions were marked immediately above the brow and spaced a little more widely apart than the equivalent lid incisions. The final incision was marked about 2 cm above the brow to create an isosceles triangle. Inserted the corneal protector. Stab incisions of 3 mm in size were made through all the marks using a BP knife no. 11. Wide subcutaneous tunnelling for cut ends of the silicone and the sleeve were done medially and laterally at the central suprabrow incision. 6/0 vicryl sutures were preplaced at this site. The silicone rod was passed through the upper central incision and exiting at lateral suprabrow incision, then lateral suprabrow incision to lateral lid margin incision and then from lateral lid margin to medial lid margin., The needle was passed upward entering at medial lid margin and exiting at medial suprabrow incision and from there exiting at central suprabrow incision. At central suprabrow incision, ends of the silicone rod were passed through the silicone sleeve and the lid height was adjusted at the level of the superior limbus. The sleeve was fixated to the frontalis muscle with the preplaced sutures. The ends of the silicone rod were shortened to 4 mm, and the cut ends were buried deep in subdermal tunnels. Subdermal approximation of wound edges was done with 6/0 vicryl. Superficial skin sutures were placed with 6/0 silk. All the other incision sites were left unsutured. Frost suture was placed in the lower lid and pulled upward and taped well to the forehead ensuring good closure of the lids. The eyes were padded. The same procedure was repeated on the other side. The patient was started on oral antibiotics and anti-inflammatory drugs postoperatively. The 1st postoperative day was uneventful, lid edema was present, cornea was clear with frost sutures intact. However, the lid closure was inadequate. The patient was discharged on the 2nd day with hourly lubricants, antibiotic drops qid, and lubricant gel in the night. A family member was taught how to tape the frost suture in the night. The patient was reviewed after a week.



Figure 1: Bilateral severe ptosis – during presentation

The patient had 6/18 vision in both eyes, lagophthalmos, and exposure keratitis inferiorly. All the incision sites were healing well. The frost sutures were removed, and the patient was advised to continue the same treatment. The patient was advised to use a copious amount of lubricant gel at the night. The lid closure was improving at 3 weeks after surgery. We reviewed the patient after 1 month. The patient's ptosis was relieved, with minimal lagophthalmos and no exposure keratiti [Figure 2]. Silk sutures were removed. The patient was advised to continue lubricant drops qid and gel hs for 6 months. We had frequent follow-up of the patient for 6 months. At 6 months, he had no lagophthalmos, and the cornea was clear. We stopped the medication. After 5 years, we reviewed the patient. His sling was intact and cornea clear with adequate lid closure [Figure 3a and b].



Figure 2: One month after frontalis sling surgery

DISCUSSION

Congenital ptosis is classified as:

- Congenital simple ptosis
- Complicated
  - With ocular abnormalities
  - Congenital cranial dysinnervation disorders (CCDDs) encompass a group of disorders resulting from anomalous innervation of the ocular and facial musculature. These disorders include
  - Duane retraction syndrome
  - Blepharophimosis ptosis epicanthus inversus syndrome
  - Congenital fibrosis of the extraocular muscles (CFEOMs) and the
  - Marcus Gunn phenomenon.[2]

CFEOM includes a group of disorders with nonprogressive restrictive ophthalmoplegia of the extraocular muscles, which are innervated by the oculomotor, trochlear, and abducent nerves manifesting with congenital blepharoptosis. Three clinical phenotypes have been distinguished. Type 1 is inherited in an autosomal dominant fashion, and the responsible gene is KIF21A, located on chromosome 12p11.2–q12, which encodes an anterograde kinesin motor protein.[4-6] The position of both eyes is below the horizontal midline with severe restriction of elevation of either eye. Type 2 CFEOM is inherited in an autosomal recessive fashion, and the responsible geneisPOX2A/ARIX, located on chromosome 11q13.1.[7] Type 3 CFEOM is inherited in an autosomal dominant fashion and is caused by a mutation in TUBB3 and KIF21A genes. This type is characterized by congenital bilateral exotropic ophthalmoplegia and ptosis, with pupillary abnormalities and manifests with ptosis, and ophthalmoplegia affecting the vertically acting extraocular muscles. This type could



Figure 3: 5 years after frontalis sling surgery (a)image in downgaze showing restriction of movement, (b) image in primary gaze position

be associated with intellectual and behavioral impairment in a few patients.[6,8-10]

In simple ptosis with poor levator function (<5 mm) with good bells phenomenon, brow suspension is indicated. Autogenous fascia lata grafts are universally recognized as the ideal material for suspension, in part due to their ability to be fully integrated with excellent take and no rejection issues. They also have a proven track record of good functional and cosmetic outcomes, and their long-term results are superior to any other nonautologous material.[11-13] However, it adds to the surgical trauma and time. Some reports have indicated that autogenous fascia and alloplastic materials resulted in similar functional and cosmetic results in frontalis suspension surgery.[14-16] Hence, synthetic materials such as mersilene mesh, nonabsorbable suture materials, polytetrafluoroethylene strip, and silicone rod are popularized.[17,18] PTFE is the material with the lowest recurrence rates as well as good cosmetic and functional results[19] but is not available here.

In ptosis with oculomotor abnormalities, it is necessary to correct the ocular motility problem before correction of ptosis because the restriction of the superior rectus and accompanying hypotropia makes the assessment of ptosis difficult. Second, the hypotropic eye with poor bells phenomenon is extremely vulnerable to exposure keratopathy due to postoperative lagophthalmos.[17] However, this patient could not afford private sector tertiary level care. Hence, we went ahead with an available better option of silicone rod.

Silicone is a polydimethylsiloxane derivative and a nonabsorbable synthetic material.[14,20,21] It is widely used due to its availability and elasticity enabling good blinking movement, easy adjustability in case of revision, or simple removal of the sling at a later date if warranted.[20] The postoperative lagophthalmos decreases as the orbicularis strengthens, and the patient eventually is able to close the operated eye.[17,18] The complications are under-correction, overcorrection, irregular lid crease, lagophthalmos, exposure keratopathy, granuloma formation, and suspension material exposure.[17,18]

Another important complication with silicone rods is a recurrence of ptosis.[22] Inadequate bond formation between the synthetic material and the surrounding tissue and cheese-wiring effect of the material were the suggested possible causes of recurred ptosis after frontalis suspension surgery.[22]

Recurrence of ptosis ranged from 7% to 44% in frontalis suspension surgery using silicone rod.[23-26] Nucci *et al*. reported that the margin reflex distance was progressively reduced by 0.6 mm within the first 3 months after surgery, and a further reduction of 0.2 mm occurred 3–12 months after frontalis suspension surgery with silicone band.[27] Lee *et al*. conducted a study on Korean pediatric patients who underwent silicone rod sling surgery and found a recurrence rate of 29.2% in bilateral cases and 11.1% in unilateral cases 3 years after surgery.[28]

Strong fixation of the silicone rod, improvement of the silicone rod's properties, and overcorrection in patients with more severe ptosis could help lower the recurrence rate after silicone rod suspension surgery in congenital ptosis.[14]

With all these facts in mind, we did a simple frontalis sling suspension. The patient had initial lagophthalmos and exposure keratitis but later on it subsided. The patient had less trauma, and it was managed with a lid surgery alone.

CONCLUSION

Congenital ptosis with restricted ocular motility is a rare condition. Simple frontalis sling surgery with a silicone rod can give good results with minimal complication and may be a cost-effective option in patients who do not have access to or cannot afford specialized care at tertiary care centers.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Pavone P, Cho SY, Praticò AD, Falsaperla R, Ruggieri M, Jin DK. Ptosis in childhood: A clinical sign of several disorders: Case series reports and literature review. Medicine (Baltimore) 2018;97:e12124.
2. Griepentrog GJ, Diehl NN, Mohney BG. Incidence and demographics of childhood ptosis. Ophthalmology 2011;118:1180-3.
3. Marenco M, Macchi I, Macchi I, Galassi E, Massaro-Giordano M, Lambiase A. Clinical presentation and management of congenital ptosis. Clin Ophthalmol 2017;11:453-63.
4. Yazdani A, Chung DC, Abbaszadegan MR, Al-Khayer K, Chan WM, Yazdani M, *et al*. A novel PHOX2A/ARIX mutation in an Iranian family with congenital fibrosis of extraocular muscles type 2 (CFEOM2). Am J Ophthalmol 2003;136:861-5.
5. Nakano M, Yamada K, Fain J, Sener EC, Selleck CJ, Awad AH, *et al*. Homozygous mutations in ARIX (PHOX2A) result in congenital fibrosis of the extraocular muscles type 2. Nat Genet 2001;29:315-20.
6. Guo S, Brush J, Teraoka H, Goddard A, Wilson SW, Mullins MC, *et al*. Development of noradrenergic neurons in the zebrafish hindbrain requires BMP, FGF8, and the homeodomain protein soulless/Phox2a. Neuron 1999;24:555-66.
7. Doherty EJ, Macy ME, Wang SM, Dykeman CP, Melanson MT, Engle EC. CFEOM3: A new extraocular congenital fibrosis syndrome that maps to 16q24.2-q24.3. Invest Ophthalmol Vis Sci 1999;40:1687-94.
8. Gutowski NJ, Bosley TM, Engle EC. 110th ENMC International Workshop: The congenital cranial dysinnervation disorders (CCDDs). Naarden, the Netherlands, 25-27 October, 2002. Neuromuscul Disord 2003;13:573-8.
9. Traboulsi EI. Congenital abnormalities of cranial nerve development: Overview, molecular mechanisms, and further evidence of heterogeneity and complexity of syndromes with congenital limitation of eye movements. Trans Am Ophthalmol Soc 2004;102:373-89.
10. Appukuttan B, Gillanders E, Juo SH, Freas-Lutz D, Ott S, Sood R, *et al*. Localization of a gene for Duane retraction syndrome to chromosome 2q31. Am J Hum Genet 1999;65:1639-46.
11. Chung HW, Seah LL. Cosmetic and functional outcomes of frontalis suspension surgery using autologous fascia lata or silicone rods in pediatric congenital ptosis. Clin Ophthalmol 2016;10:1779-83.
12. Leibovitch I, Leibovitch L, Dray JP. Long-term results of frontalis suspension using autogenous fascia lata for congenital ptosis in children under 3 years of age. Am J Ophthalmol 2003;136:866-71.
13. Yoon JS, Lee SY. Long-term functional and cosmetic outcomes after frontalis suspension using autogenous fascia lata for pediatric congenital ptosis. Ophthalmology 2009;116:1405-14.
14. Kim CY, Son BJ, Son J, Hong J, Lee SY. Analysis of the causes of recurrence after frontalis suspension using silicone rods for congenital ptosis. PLoS One 2017;12:e0171769.
15. Wasserman BN, Sprunger DT, Helveston EM. Comparison of materials used in frontalis suspension. Arch Ophthalmol 2001;119:687-91.
16. Ben Simon GJ, Macedo AA, Schwarcz RM, Wang DY, McCann JD, Goldberg RA. Frontalis suspension for upper eyelid ptosis: Evaluation of different surgical designs and suture material. Am J Ophthalmol 2005;140:877-85.
17. Garg A, Alio JL. Surgical Techniques in Ophthalmology: Oculoplasty and Reconstructive Surgery. Jaypee brothers medical publishers. 2010;396-400.
18. Tyers AG, Collin JR. Colour Atlas of Ophthalmic Plastic Surgery. Churchill Livingstone1995;150-9.
19. Pacella E, Mipatrini D, Pacella F, Amorelli G, Bottone A, Smaldone G, *et al*. Suspensory materials for surgery of blepharoptosis: A systematic review of observational studies. PLoS One 2016;11:e0160827.
20. Shah KP, Mukherjee B. Efficacy of frontalis suspension with silicone rods in ptosis patients with poor Bell's phenomenon. Taiwan J Ophthalmol

2017;7:143-8.
21. Wagner RS, Mauriello JA Jr., Nelson LB, Calhoun JH, Flanagan JC, Harley RD. Treatment of congenital ptosis with frontalis suspension: A comparison of suspensory materials. Ophthalmology 1984;91:245-8.
22. Buttanri IB, Serin D, Karslioglu S, Akbaba M, Ari S, Fazil K. Effect of suturing the silicone rod to the tarsal plate and the suture material used on success of frontalis suspension surgery. Ophthalmic Plast Reconstr Surg 2013;29:98-100.
23. Ben Simon GJ, Macedo AA, Schwarcz RM, Wang DY, McCann JD, Goldberg RA. Frontalis suspension for upper eyelid ptosis: Evaluation of different surgical designs and suture material. Am J Ophthalmol 2005;140:877-85.
24. Carter SR, Meecham WJ, Seiff SR. Silicone frontalis slings for the correction of blepharoptosis: Indications and efficacy. Ophthalmology 1996;103:623-30.
25. Hersh D, Martin FJ, Rowe N. Comparison of silastic and banked fascia lata in pediatric frontalis suspension. J Pediatr Ophthalmol Strabismus 2006;43:212-8.
26. Bernardini FP, de Conciliis C, Devoto MH. Frontalis suspension sling using a silicone rod in patients affected by myogenic blepharoptosis. Orbit 2002;21:195-8.
27. Nucci P, Lembo A, Santangelo E, Fogagnolo P, Serafino M. Five-year follow-up of a 30-month trial of stability of silicone band frontalis suspension for the treatment of severe unilateral upper eyelid ptosis in infants. Semin Ophthalmol 2016;31:215-8.
28. Lee MJ, Oh JY, Choung HK, Kim NJ, Sung MS, Khwarg SI. Frontalis sling operation using silicone rod compared with preserved fascia lata for congenital ptosis a three-year follow-up study. Ophthalmology 2009;116:123-9.

Case Report

Herpes simplex virus-1 associated third cranial nerve palsy in pediatric age group

ABSTRACT

A 4-year-old female patient presented with drooping of the right upper eyelid of 10 days duration. There was a history of low grade fever 15 days ago which subsided with the use of oral paracetamol. Abnormal head posture with mild upper lid ptosis was noted on right side. Right pupil was fixed and mid-dilated. She was diagnosed with right-sided third cranial nerve palsy. Serum and cerebrospinal fluid samples were positive for IgM antibodies to herpes simplex virus-1. The patient was treated with systemic steroids and anti-virals. The patient responded well to treatment, and there was complete resolution of ocular signs 45 days after presentation.

Keywords: Demyelinating, herpes simplex virus, pediatric, third cranial nerve palsy

INTRODUCTION

Cranial nerve palsies in childhood are a rare entity and mostly involve third, fourth and sixth cranial nerves, with an incidence of 7.6/10000.[1] Third cranial nerve palsy is uncommon in children, and its causes are different from that found in the adult age group. Many pediatric series have shown that adverse intrauterine events and or traumatic delivery and postnatal trauma to be the most common causes of congenital third cranial nerve palsy with other etiologies being of tumor or vascular origin.[2,3] Infection as a cause is also not rare among which upper respiratory tract infections, meningitis, encephalitis, Varicella, and orbital inflammations such as Tolosa hunt syndrome are commonly seen.[4] Therefore, a detailed neurological assessment is indicated to rule out the possible causes in such a patient. The management also varies according to the cause, extent of palsy, and amount of recovery with or without aberrant regeneration.

We report an unusual case of unilateral third cranial nerve palsy in a 4-year-old child due to postinfective demyelination with herpes simplex virus-1 (HSV-1) as the etiology.

Submitted: 15-Aug-2021 **Revised:** 03-Sep-2021
Accepted: 10-Sep-2021 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	Quick Response Code
DOI: 10.4103/kjo.kjo_178_21	

CASE REPORT

A 4-year-old female presented to our outpatient department with drooping of the right upper lid for 10 days. There was no associated history of headache, vomiting, trauma, or recent vaccination. The patient had low grade fever 15 days back which lasted for 3 days and was relieved by taking oral paracetamol.

On examination, visual acuity in both eyes was 20/20. Abnormal head posture (right-sided head tilt and chin up) and right upper lid mild ptosis was present [Figure 1]. Right eyeball was in down and out position with restricted

Suchismita Mishra, Lipika Mehra, Pradeep Kumar Panigrahi, Lulup Kumar Sahoo[1]

Departments of Ophthalmology and [1]Neurology, Institute of Medical Sciences and SUM Hospital, Siksha "O" Anusandhan (Deemed to be) University, Bhubaneswar, Odisha, India

Address for correspondence: Dr. Pradeep Kumar Panigrahi, Department of Ophthalmology, Institute of Medical Sciences and SUM Hospital, Siksha "O" Anusandhan (Deemed to be) University, 8-Kalinga Nagar, Bhubaneswar - 751 003, Odisha, India.
E-mail: doc.pkp25@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Mishra S, Mehra L, Panigrahi PK, Sahoo LK. Herpes simplex virus-1 associated third cranial nerve palsy in pediatric age group. Kerala J Ophthalmol 2023;35:215-7.



Figure 1: Clinical photograph of the patient at presentation showing mild ptosis in the right upper lid with eye fixed in down and out position



Figure 2: Clinical photograph of the patient 45 days after presentation showing complete resolution of ptosis with orthotropia in primary gaze

elevation, adduction, and depression while left eye ocular movements were full and adequate in all directions. Pupil in the right eye was mid dilated and fixed. Rest anterior and posterior segment examination of both eyes was unremarkable. We diagnosed it as a case of right third cranial nerve palsy.

Systemic examination of the patient revealed no neurological abnormality, and none of the other cranial nerves were affected. Gadolinium-enhanced magnetic resonance imaging was performed to exclude other causes of third nerve palsy where no pathology was noted. The patient was referred to a neurologist for detailed examination where a lumbar puncture was done and cerebrospinal fluid (CSF) was sent for cytology, biochemistry, adenosine deaminase, Gram stain, and Giemsa stain which were all within normal limits. All routine blood investigations were normal. Serum and CSF samples were also sent for the detection of viral markers where IgM antibody to HSV-1 was positive.

Since the patient was clinically stable and CSF analysis had no signs suggestive of recent infection, a presumptive diagnosis of postinfective demyelination was made. She was started on intravenous methylprednisolone at 30 mg/kg/day for 5 days followed by oral prednisolone in tapering doses over 1 month and intravenous acyclovir at 10 mg/kg/day 8 hourly for 14 days. The patient was reviewed after 10 days where the signs of improvement were seen and on 45 days follow-up, we noticed full resolution of third nerve palsy without any signs of aberrant regeneration or abnormal head posture [Figure 2].

DISCUSSION

Cranial mononeuropathies are more commonly associated with varicella zoster infection but uncommon after HSV-1 infection except for reports where it was associated with Bell's palsy.[5] It has been consistently reported that HSV-1 persists as latent infection in trigeminal, geniculate, and vestibular ganglion and its reactivation commonly causes recurrent painful epithelial erosions along a dermatome. However, its pathogenesis in central nervous system (CNS) infections is still less known. It can migrate from sensory ganglion to CNS and is presumed to cause focal encephalitis in temporal lobes usually after reinfection or reactivation or can occur as an immune mediated disease.[6]

Genomic HSV-1 DNA has been isolated from oculomotor nuclei in the brain stem and can be a possible mechanism for the related oculomotor palsy.[7] HSV-1 has also been reported to cause demyelination of nerve fibers by affecting the oligodendrocytes.[8] Third cranial nerve palsy associated with HSV-1 has been reported in two cases previously in adult age group where both patients had presented with unilateral third cranial nerve palsy and no other pathology could be detected, but there was a previous history of herpes simplex in the form of vesicles few years back.[9] No such history was given by our patient. Serum and CSF antibodies to HSV-1 were positive in that case report which was consistent with our case.

Systemic steroids have been established to play an important role in postinfectious neurological sequelae in the pediatric age group.[10] Our patient was treated with systemic antivirals since IgM antibodies were positive, although no other signs of active infection were seen. Systemic steroids were added to treat any amount of inflammation or demyelination which may have occurred postinfection. The patient responded very well to the treatment, and full resolution was witnessed within 45 days.

CONCLUSION

To conclude, such a case of third nerve palsy with evidence of HSV-1 is uncommon. To the best of our knowledge, this is the first case of HSV-1-associated third cranial nerve palsy in the pediatric age group. This case adds to the body of the literature available on HSV-1 associated cranial nerve palsies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Holmes JM, Mutyala S, Maus TL, Grill R, Hodge DO, Gray DT. Pediatric third, fourth, and sixth nerve palsies: A population-based study. Am J Ophthalmol 1999;127:388-92.
2. Ng YS, Lyons CJ. Oculomotor nerve palsy in childhood. Can J Ophthalmol 2005;40:645-53.
3. Schumacher-Feero LA, Yoo KW, Solari FM, Biglan AW. Third cranial nerve palsy in children. Am J Ophthalmol 1999;128:216-21.
4. Keith CG. Oculomotor nerve palsy in childhood. Aust N Z J Ophthalmol 1987;15:181-4.
5. McCormick DP. Herpes simplex virus as a cause of Bell's palsy. 1972. Rev Med Virol 2000;10:285-9.
6. Kennedy PG, Chaudhuri A. Herpes simplex encephalitis. J Neurol Neurosurg Psychiatry 2002;73:237-8.
7. Kristensson K, Svennerholm B, Vahlne A, Nilheden E, Persson L, Lycke E. Virus-induced demyelination in herpes simplex virus-infected mice. J Neurol Sci 1982;53:215-6.
8. Theil D, Horn AK, Derfuss T, Strupp M, Arbusow V, Brandt T. Prevalence and distribution of HSV-1, VZV, and HHV-6 in human cranial nerve nuclei III, IV, VI, VII, and XII. J Med Virol 2004;74:102-6.
9. Sekizawa T, Nakamura S, Kogure K, Hayashi K, Yanagi K, Openshaw H. Idiopathic third cranial nerve palsy associated with herpes simplex virus infection. Br Med J (Clin Res Ed) 1987;295:813.
10. Bozzola E, Spina G, Valeriani M, Papetti L, Ursitti F, Agostiniani R, *et al.* Management of pediatric post-infectious neurological syndromes. Ital J Pediatr 2021;47:17.

Case Report

Bilateral giant dacryocele in a case of Tessier cleft-3

ABSTRACT

Tessier cleft-3 represents diverse clinical presentations, from simple notch in nasolabial groove to bilateral forms with cranial extensions. We report a 10-year-old child with facial features of Tessier cleft-3 and associated epiphora due to an abnormally dilated nasolacrimal duct on imaging. No previous associations of giant dacryocoeles have ever been reported.

Keywords: Congenital nasolacrimal duct obstruction, dacryocoeles, facial cleft disorder, Tessier cleft-3

INTRODUCTION

Tessier developmental cleft anomalies are infrequent situations. The nature and extent of the anomaly vary according to the cleft number. Here, we report a bilateral dacryocoele in a case of Tessier cleft-3, which to the best of our knowledge, has never been reported.

CASE REPORT

A 10-year-old child presented to the outpatient department with the complaints of watering from both eyes from 1 year of age. There was also a history of swelling on either side of the nasal bridge, which on pressing expressed pus from the medial aspect of the eyes and subsequently reduced in size. He was born of a normal-term vaginal delivery, and the mother had no significant antenatal event.

On general examination, he was alert, conscious, and oriented. He had a high-arched palate, with bilateral malar hypoplasia with areas of patchy pigmentation, high angulation of angle of the nose, flat nasal bridge, and polydactyly in the right hand.

On ophthalmological examination, there was bilateral microphthalmos and a left convergent squint with a visual acuity of 6/12 in the right and 1/60 in the left eye. Antimongoloid slant could be appreciated, and intercanthal distance was measured to be 36 mm. The regurgitation test was positive in both eyes, which was confirmed by the presence of mucopurulent discharge on applying pressure over the lacrimal sac area [Figure 1].

On slit-lamp examination, the right corneal diameter was measured to be 10.5 mm × 11 mm and that in the left eye was 7.5 mm × 8.5 mm. A typical iris coloboma with a pear-shaped pupil was present on the left side. Fundus examination also revealed a fundal coloboma on the left side. Routine blood investigations were carried out, which came out to be normal. Contrast-enhanced computed tomography orbit was done, which showed unusually dilated nasolacrimal ducts [Figure 2].

A diagnosis of bilateral Tessier cleft-3 with bilateral congenital nasolacrimal duct obstruction (NLDO) with giant dacryocoele was made, and he was planned for external dacryocystorhinostomy with bicanalicular stent placement. Six weeks following the surgery, the symptoms had subsided.

Sahil Agrawal[1,2], Sujeeth Modaboyina[1,2], Saloni Gupta[3], Deepsekhar Das[1,2]

[1]Dr. Rajendra Prasad Centre for Ophthalmic Sciences, [2]Oculoplasty and Ocular Oncology Services, All India Institute of Medical Sciences, [3]Department of Ophthalmology, Northern Railway Central Hospital, New Delhi, India

Address for correspondence: Dr. Deepsekhar Das, Oculoplasty and Orbital Tumor Services, Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi - 110 029, India.
E-mail: doc.deep.das@gmail.com

Submitted: 26-Nov-2021 **Revised:** 02-Jan-2022
Accepted: 22-Jan-2022 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	Quick Response Code
DOI: 10.4103/kjo.kjo_221_21	

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Agrawal S, Modaboyina S, Gupta S, Das D. Bilateral giant dacryocele in a case of Tessier cleft-3. Kerala J Ophthalmol 2023;35:218-9.



Figure 1: Clinical picture of the patient with bilateral Tessier cleft-3 showing bilateral malar hypoplasia with areas of patchy pigmentation, high angulation of angle of the nose, and flat nasal bridge

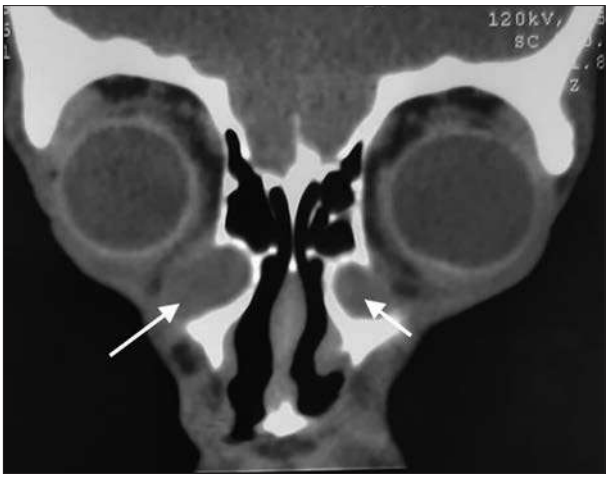


Figure 2: Contrast-enhanced computed tomography head, orbit, and paranasal sinuses showing bilateral enlarged nasolacrimal duct

DISCUSSION

In 1976, to easily identify the position, Tessier classified various types of clefts (facial, craniofacial, and laterofacial) by numbering them from 0 to 14 counterclockwise around the orbit. Of which, Tessier cleft-3 is characterized by cleft lip and palate, the base of nasal alae superiorly displaced, medial canthus inferiorly placed, lower eyelid coloboma, nasolacrimal abnormality, telorbitism, disruption of the medial wall of the antrum, and cleft of the inferomedial wall of the orbit.[1]

The most accepted theory of cleft formation is believed to be the failure of mesoderm fusion between the lateral nasal process (from the frontonasal process) and the maxillary process. Another theory states that due to tissue destruction caused by amniotic bands, the occurrence of orbital clefts takes place.[2] The defenders of the first theory believe a band-related mechanism cannot explain some of the features such as cleft palate, anophthalmia, and microphthalmia, which, however, can be described by focal fetal dysplasia. In bilateral symmetrical clefts, the pattern of cleft, with slight variations, is usually consistent and cannot be explained by randomly distributed bands. However, some associated deformities caused by bands include constriction rings, visceral, and extremity defects.[3,4]

Commonly associated ocular anomalies with Tessier cleft-3 are colobomatous eyelids, hypertelorism, microphthalmia, punctal or canalicular agenesis, NLDO, and exstrophy. However, bilateral dacryocoeles in Tessier cleft have never been reported.[3-7] The presence of NLDO in this patient with Tessier type-3 may be attributed to the concurrent timing of embryological events during the formation of clefts which is usually between 5th and 16th weeks of gestation. The management of Tessier clefts depends upon the extent of the cleft. In the case of a cleft lip and cleft palate, adequate plastic reconstruction should be carried out.[6] However, in a situation like that of our patient, where the degree of the cleft was limited to the lacrimal drainage system, an external dacryocystorhinostomy yields great results.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Tessier P. Anatomical classification facial, cranio-facial and latero-facial clefts. J Maxillofac Surg 1976;4:69-92.
2. Whitaker LA, Katowitz JA, Randall P. The nasolacrimal apparatus in congenital facial anomalies. J Maxillofac Surg 1974;2:59-63.
3. Gawrych E, Janiszewska-Olszowska J, Chojnacka H. Tessier type 3 oblique facial cleft with a contralateral complete cleft lip and palate. Int J Oral Maxillofac Surg 2010;39:1133-6.
4. Allam KA, Lim AA, Elsherbiny A, Kawamoto HK. The Tessier number 3 cleft: A report of 10 cases and review of literature. J Plast Reconstr Aesthet Surg 2014;67:1055-62.
5. Das D, Rathod A, Gupta S, Modaboyina S, Agrawal S. Isolated unilateral Tessier cleft 10 with anterior staphyloma. Korean J Ophthalmol 2021;35:244-5.
6. Singh S, Sharma A, Mittal V, Ali MJ. Lacrimal drainage anomalies in Tessier cleft 3 with unilateral anophthalmos. Eur J Ophthalmol 2021;31:P12-4.
7. Agrawal S, Modaboyina S, Gupta S, Das D. Asyndromic isolated unilateral Tessier cleft 8 with euryblepharon. BMJ Case Rep 2021;14:e245548.

Case Report

A conventional case of herpes zoster ophthalmicus with curious findings

ABSTRACT

A 49-year-old female presented with complaints of right-sided headache, right eye severe pain, and diminution of vision since 1 month. Examination revealed healed skin rashes over the right side of the forehead, right upper lid mechanical ptosis, unilateral restriction of movements, corneal edema, total hyphema, and thickening of retino-choroido-scleral (RCS) complex with subtenon fluid on ultrasonography. A diagnosis of herpes zoster uveitis with total hyphema with posterior scleritis was considered. She was started on topical steroids and intraocular pressure (IOP) lowering agents. But, she was lost to follow up and 6 months later, the eye was phthisical. Here, we present a relatively rare case of herpes zoster ophthalmicus (HZO) with hyphema and posterior scleritis.

Keywords: Herpes zoster ophthalmicus, hyphema, ocular hypertension, scleritis

INTRODUCTION

Herpes zoster ophthalmicus (HZO) occurs as a result of the reactivation of the varicella-zoster virus, involving the ophthalmic division of the trigeminal nerve. The most common ocular manifestations of HZO are keratitis, conjunctivitis, and anterior uveitis.[1]

Hyphema, scleritis, and orbital apex syndrome are unusual complications of HZO.[2,3] Erythematous macules appear on the forehead and along the distribution of the ophthalmic nerve.[4] The involvement of the tip of the nose representing the dermatome of a nasociliary nerve is classically known as Hutchinson's sign. Ocular involvement is more common in such cases, and hence, urgent ophthalmological consultation is required.[5]

We report a case of HZO with hyphema with posterior scleritis.

CASE REPORT

A 49-year-old female presented with complaints of right-sided headache with severe pain and diminution of vision in the right eye since 1 month. She was on oral valacyclovir 1 g TID as per the dermatologist's precision. Examination showed healed vesicular skin rashes over the right forehead and tip of the nose [Figure 1]. Visual acuity was the perception of light and examination revealed upper lid ptosis with edema, uniocular movement restriction, conjunctival congestion, corneal edema, and total anterior chamber hyphema [Figure 2]. The left eye was normal.

Intraocular pressure (IOP) was 26 mm of Hg with applanation tonometry. Ultrasonography revealed retino-choroido-scleral (RCS) complex thickening with subtenon fluid [Figure 3].

She was diagnosed with HZO with total hyphema with posterior scleritis. Blood investigations (full blood count, erythrocyte sedimentation rate, fasting blood sugar, and C-reactive protein) were within normal limits.

Submitted: 24-Sep-2022 **Revised:** 01-Dec-2022
Accepted: 05-Dec-2022 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	Quick Response Code
DOI: 10.4103/kjo.kjo_105_22	

Aravind Yaragani, Kamala Subramanian
Glaucoma Services, Sankara Eye Hospital, Shimoga, Karnataka, India

Address for correspondence: Dr. Aravind Yaragani, Fellow Glaucoma Services, Sankara Eye Hospital, Harakere, Shimoga - 577 202, Karnataka, India.
E-mail: aravindyaragani@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Yaragani A, Subramanian K. A conventional case of herpes zoster ophthalmicus with curious findings. Kerala J Ophthalmol 2023;35:220-2.

Topical prednisolone acetate (1%) 4 hourly, homatropine (2%) 12 hourly, brimonidine (0.2%) + timolol (0.5%) 12 hourly, dorzolamide (2%) 8 hourly, topical acyclovir ointment 5 times/day, oral acetazolamide 250 mg 12 hourly, oral tranexamic acid 500 mg 12 hourly were started.

At the 1-week follow-up, there was no improvement in vision, but the pain and headache subsided. Ocular movements were restricted; IOP was 20 mm of Hg. On examination, there was settled hyphema in the anterior chamber with blood-stained aqueous, iris, pupil, and lens details not clear. She was advised to continue the same treatment with tapering of topical steroids and review after 1 week.

Unfortunately, she was lost to follow-up and after 6 months, examination revealed a very soft globe, normal ocular movements, pigmented keratic precipitates over corneal endothelium with superficial vascularization of the cornea, and posterior synechiae with complicated cataract [Figure 4]. IOP was 4 mm Hg in the right eye. The fundus was not visualized. On ultrasonography, there was RCS thickening with minimal subtenon fluid.

DISCUSSION

Herpetic anterior uveitis is the most common cause of viral anterior uveitis accounting for 5–10% in the western world[6] and 0.9–8.3% in India.[7] Ophthalmic involvement of HZO may be diverse which includes eyelid rash, conjunctivitis, punctate epithelial keratitis, pseudo dendrites, anterior stromal keratitis, disciform keratitis, raised IOP, anterior uveitis, episcleritis, and acute retinal necrosis in 50% of patients.[1]

Hyphema and posterior scleritis are rare manifestations of herpes zoster.[8,9] In cases of herpes zoster uveitis with



Figure 1: Shows the healed vesicular lesions on the forehead and tip of the nose of the patient associated with pigmentation. The involved eye also had upper lid ptosis and extraocular muscle restriction

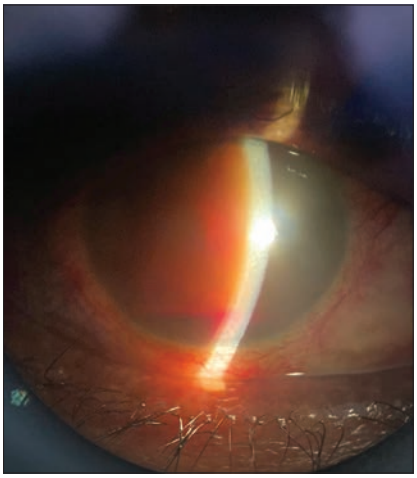


Figure 2: Slit lamp photograph of the right eye of the patient showing a total anterior chamber hyphema with corneal edema and circumcorneal congestion

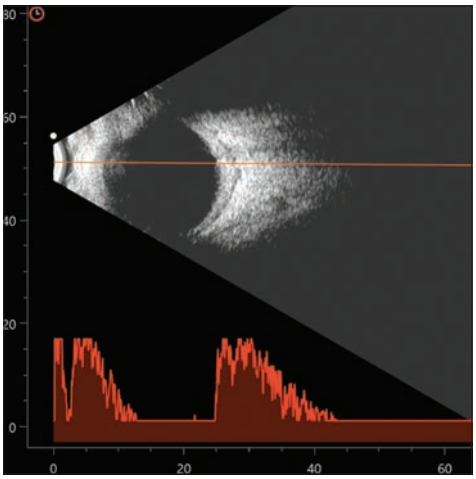


Figure 3: Shows the ultrasonography B-scan of the patient's right eye with an A-scan overlay. A thickened retino-choroido-scleral complex along with a hypoechoic space behind the sclera suggests the presence of subtenon fluid

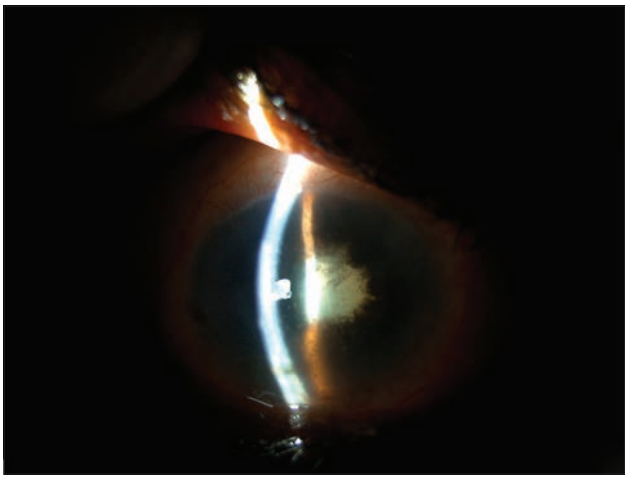


Figure 4: Shows the slit lamp photograph of the anterior segment. Old keratic precipitates on endothelium with corneal vascularization can be seen. The above image also depicts a complicated cataract with posterior synechiae

hyphema, it is widely believed that hyphema is caused by occlusive vasculitis to the iris leading to ischemia and bleeding into the anterior chamber.[4,10] Studies suggest that the pathophysiological mechanism of posterior scleritis is proposed to be direct invasion and host immune reaction to the virus particles.

Hyphema shows a drastic reduction on initiation of prednisolone,[9] and a similar finding was noted in our case. An iris fluorescein angiography would be helpful to rule out rubeosis as a cause of hyphema.[8] In view of severe hyphema, we could not do this in our patient. An uncommon complication associated with HZO is scleritis, which generally presents as anterior scleritis. Only a few cases of posterior scleritis associated with HZO have been reported in the literature. Although posterior scleritis is generally associated with underlying autoimmune diseases, rare infectious etiologies such as Lyme disease, herpes zoster virus, or tuberculosis also have been reported.

The total hyphema in our patient precluded a fundoscopic examination and B-scan ultrasonography revealed a unilaterally thickened sclera consistent with posterior scleritis.

CONCLUSION

Hyphema and posterior scleritis in herpes zoster anterior uveitis are rare presentations. Hyphema in iridocyclitis is a pointer towards herpes zoster etiology in a patient with skin lesions. Early referral of herpes zoster patients to the ophthalmologist is vital to detect and give appropriate treatment for ocular manifestations to preserve vision.

Acknowledgement

I would like to express my sincere gratitude to Dr. Kamala Subramanian, consultant of glaucoma services and Dr. Pradeep Sagar, consultant of vitreo retina services at Sankara Eye Hospital, Shimoga for their invaluable guidance and encouragement in the successful completion of this case report.

Declaration of patient consent

Written and signed informed consent from the patient has been obtained.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Yawn BP, Wollan PC, StSauver JL, Butterfield LC. Herpes zoster eye complications: Rates and trends. Mayo Clin Proc 2013;88:562-70.
2. Sanjay S, Chan EW, Gopal L, Hegde SR, Chang BC. Complete unilateral ophthalmoplegia in herpes zoster ophthalmicus, J. Neuroophthalmol 2009;29:325-37.
3. Fong DS, Raizman MB. Spontaneous hyphema associated with anterior uveitis. Br J Ophthalmol 1993;77:635-8.
4. Saad S, Christopher TA. Evaluation and management of herpes zoster ophthalmicus. Am Fam Physician 2002;66:1723-30.
5. Frary J, Petersen PT, Pareek M. Hutchinson's sign of ophthalmic zoster. Clin Case Rep 2020;8:219-20.
6. Cunningham ET. Jr. Diagnosing and treating herpetic anterior uveitis. Ophthalmology 2000;107:2129-30.
7. Babu K, Kini R, Philips M, Subbakrishna DK. Clinical profile of isolated viral anterior uveitis in a South Indian patient population. Ocul Immunol Inflamm 2014;22:356-9.
8. Hayasaka S, Watanabe M, Yamamoto Y, Noda S, Sekimoto M, Setogawa T. Herpes Zoster opthalmicus complicated by hyphema and haemorrhagic glaucoma. Ophthalmologica 1988;196:185-7.
9. Okunuki Y, Sakai J, Kezuka T, Goto H. A case of Herpes Zoster uveitis with severe hyphema. BMC Ophthalmol 2014;14:74-7.
10. Babu K, Konana VK, Ganesh SK, Patnaik G, Chan NS, Chee SP, *et al*. Viral anterior uveitis. Indian J Ophthalmol 2020;68:1764-73.

Case Report

A rare case of central retinal artery occlusion following severe orbital blowout fracture

ABSTRACT

A 16-year-old male presented with sudden-onset loss of vision in the left eye (LE) 2 weeks following a road traffic accident. Clinical and radiological investigations lead to a diagnosis of orbital blowout fracture with central retinal artery occlusion in LE. Central retinal artery occlusion is a rare complication occurring simultaneously with an orbital blowout fracture and is associated with a very poor prognosis.

Keywords: Blowout fracture, central retinal artery occlusion, orbit, trauma

INTRODUCTION

Central retinal artery occlusion (CRAO) is a vascular disorder of embolic origin commonly. CRAO as a complication following trauma, retrobulbar injections, orbital surgeries, etc., has been reported in the literature.[1-4] Simultaneous presentation of CRAO with a blowout fracture of the orbit is very rare.[5] We report a very rare case of an orbital blowout fracture complicated with CRAO.

CASE REPORT

A 16-year-old healthy male presented in the department of ophthalmology with sudden-onset painful loss of vision in the left eye (LE) of 2 weeks' duration. The patient gave a history of having been involved in a road traffic accident 2 weeks back. He had undergone primary treatment elsewhere. On examination, best-corrected visual acuity in the right eye (RE) was 6/9, N6. Perception of light (PL) was absent in LE Anterior segment examination of the RE was within the normal limits. Examination of the LE showed periorbital edema, enophthalmos, and gross restriction of ocular movements in all directions of gaze. Slit-lamp examination of the LE revealed clear cornea with normal anterior chamber depth and clear lens. The pupil was mid dilated, circular, and not reacting to light. Intraocular pressure measured using noncontact tonometer was 17 and 13 mmHg. Fundoscopy of the RE showed clear media with an area of subretinal hemorrhage temporal and inferior to optic disc [Figure 1a]. Indirect ophthalmoscopy of the LE revealed clear media, gross retinal whitening in the macular area, cherry red spot, few intraretinal macular hemorrhages, and narrowing of the retinal arterioles [Figure 1b]. Optical coherence tomography (OCT) of the LE showed hyper-reflective inner retinal layers causing shadowing of the outer retina [Figure 2]. OCT of the RE showed normal foveal contour. The patient had already undergone radiological investigations elsewhere. Three-dimensional computed tomography of the skull showed multiple facial bone fractures and fracture of medial, lateral, roof, and floor of the left orbit. Magnetic resonance imaging of the brain showed enophthalmos with blowout fracture of the inferior wall of the left orbit with herniation of

Pradeep Kumar Panigrahi, Anita Minj, Priya Gupta, Lipika Mehra

Department of Ophthalmology, Institute of Medical Sciences and SUM Hospital, Siksha "O" Anusandhan University, Bhubaneswar, Odisha, India

Address for correspondence: Dr. Pradeep Kumar Panigrahi, Department of Ophthalmology, Institute of Medical Sciences and SUM Hospital, Siksha "O" Anusandhan University, 8-Kalinga Nagar, Bhubaneswar - 751 003, Odisha, India.
E-mail: doc.pkp25@gmail.com

Submitted: 27-Feb-2021 **Revised:** 02-Mar-2021
Accepted: 09-Mar-2021 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	Quick Response Code
DOI: 10.4103/kjo.kjo_53_21	

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Panigrahi PK, Minj A, Gupta P, Mehra L. A rare case of central retinal artery occlusion following severe orbital blowout fracture. Kerala J Ophthalmol 2023;35:223-5.

intraorbital contents into the left maxillary sinus [Figure 3a]. Left intraorbital hematoma causing compression of the optic nerve was also noted [Figure 3b]. A diagnosis of orbital blowout fracture with central retina artery occlusion in LE was made. Poor visual prognosis was explained for LE. The patient was given the option of repair of the orbital fracture, but the patient refused any surgical intervention.

DISCUSSION

Spontaneous CRAO is a rare ocular complication of either embolic, thrombotic, sclerotic, or other systemic origins. Visual acuity at presentation is usually very poor and a pale retina with arterial narrowing and cherry red spot is seen clinically during the acute phase. All the above findings were present in our case helping us in making the diagnosis of CRAO. Orbital blowout fracture is a common complication following severe blunt trauma and usually causes diplopia due to entrapment of extraocular muscles. It is very rare to have a simultaneous blowout fracture with CRAO. Himori *et al*.[5] have reported a case of an orbital blowout fracture with CRAO in a 20-year-old female following a road traffic accident. The patient had no PL at presentation. Surgery was done for the orbital fracture and the patient had a vision of PL only 4 months after surgery. Emery *et al*.[6] have reported a case of an orbital blowout fracture which underwent surgical repair on the 9th day following presentation. However, in their case, CRAO developed as a complication after surgery.

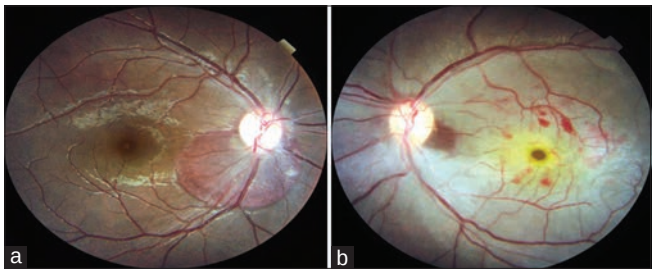


Figure 1: (a) Color fundus photograph of the right eye showing subretinal hemorrhage inferior and temporal to the optic disc. (b) Color fundus photograph of the left eye showing acute central retinal artery occlusion

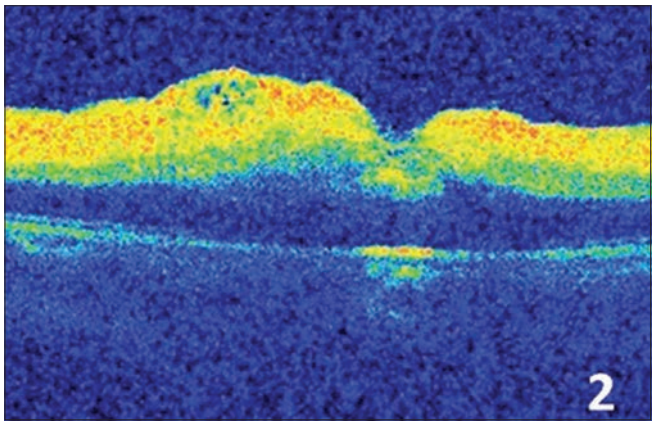


Figure 2: Optical coherence tomography image of the left eye showing hyper-reflective inner retinal layers with shadowing of the outer retina

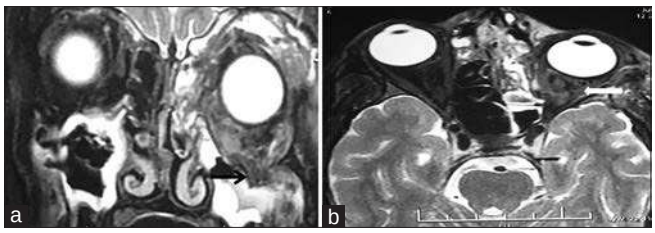


Figure 3: (a) Magnetic resonance imaging showing orbital blowout fracture of the left eye with herniation of intraocular contents into the left maxillary sinus (black arrow). (b) Magnetic resonance imaging showing left orbital hematoma within the intraconal compartment (white arrow)

Pathogenesis of CRAO following trauma includes raised intraocular pressure, injury to optic nerve, or mechanical stress. The orbit is a relatively closed compartment and any hemorrhage can lead to a significant increase in mechanical pressure which can lead to CRAO.[7] There was radiological evidence of orbital hematoma within the intraconal compartment in our case. This along with the compression resulting from the fractured orbital walls might have resulted in CRAO in our case. The efficacy of decompression surgery following trauma is uncertain.[7] Our patient presented 2 weeks following trauma. Any surgery following such a long interval would not have resulted in much improvement of vision. Our patient did not opt for any surgical interventions because of financial constraints and poor visual prognosis associated with the case.

To conclude, CRAO can be a very rare complication following an orbital blowout fracture. To the best of our knowledge, this is the second such report of orbital blowout fracture with simultaneous CRAO. This report adds to the body of literature available on CRAO following blunt trauma.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Vinerovsky A, Rath EZ, Rehany U, Rumelt S. Central retinal artery occlusion after peribulbar anesthesia. J Cataract Refract Surg 2004;30:913-5.
2. Cumurcu T, Doganay S, Demirel S, Cankaya C. Traumatic optic neuropathy and central retinal artery occlusion following blunt ocular trauma. J Clin Med Res 2011;3:55-7.
3. Chong CC, Chang AA. Traumatic optic nerve avulsion and central retinal artery occlusion following rugby injury. Clin Exp Ophthalmol 2006;34:88-9.
4. Filev F, Atiskova Y, Klemm M. Central arterial occlusion after blunt force ocular injury: Case report. Ophthalmologe 2017;114:159-62.
5. Himori N, Kunikata H, Otomo T, Fuse N, Nishida K. Central retinal artery occlusion following severe blow-out fracture in young adult. Clin Ophthalmol 2009;3:325-8.
6. Emery JM, Huff JD, Justice J Jr. Central retinal artery occlusion after blow-out fracture repair. Am J Ophthalmol 1974;78:538-40.
7. Linberg JV. Orbital compartment syndromes following trauma. Adv Ophthalmic Plast Reconstr Surg 1987;6:51-62.

Bilateral persistent pupillary iris membrane mimicking chronic anterior uveitis

An 18-year-old female patient presented in the outpatient department (OPD) with chief complaints of pain and a foreign body sensation in her right eye, which was not associated with decreased vision, for two days. There was no history of trauma, intraocular surgery, or recurrent similar episodes in the past in the right eye. The best-corrected distance visual acuity in both eyes was 6/6 on the Snellen chart. Slit-lamp examination of both eyes revealed multiple follicles in the inferior conjunctival fornix. After pupil dilation, we found an irregular pupillary margin with multiple bands of iris tissue extending from the 11 o'clock to 3 o'clock position and 10 o'clock to 12 o'clock position in the right and left eye, respectively [Figure 1a and b]. Bands of iris strands were attached to the anterior capsule of the lens [Figure 2]. No pigment dispersion was seen on the endothelium and in the iridocorneal angles on gonioscopy. At first impression, the iris bands looked like posterior synechiae. However, slit-lamp examination showed no keratic precipitates, iris atrophy, or iris nodules. On enquiry, the patient's parents informed us that some other doctor had informed them that the iris bands were present since birth in both eyes of the patient. Careful history and clinical signs helped us rule out persistent pupillary iris membrane from chronic anterior uveitis.

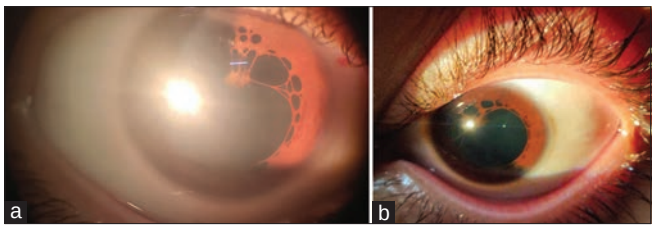


Figure 1: (a) Slit-lamp picture of the right eye shows persistent pupillary membrane extending from the 11 o'clock to 3 o'clock position. (b) Slit-lamp picture of the left eye shows persistent pupillary membrane extending from the 10 o'clock to 12 o'clock position

Submitted: 18-Jul-2022 **Revised:** 02-Sep-2022
Accepted: 05-Oct-2022 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	Quick Response Code
DOI: 10.4103/kjo.kjo_86_22	

CLINICAL SIGNS IN OUR CASE

- Bilateral, symmetrical, fine iris strands along the collarette
- Bilateral iris bands attached to the anterior capsule of the lens (type 2 membranes)

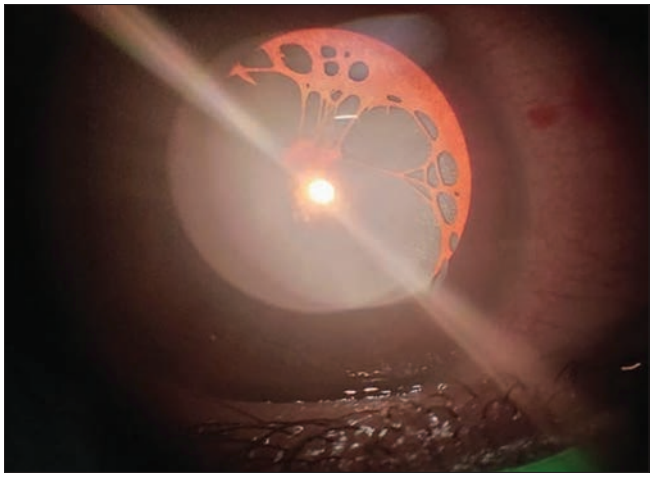


Figure 2: Slit-lamp picture of the right eye shows persistent pupillary membrane attached to the anterior capsule of the lens

Amol Ganvir, Aryamol V. Surendran, Shruti Shirwadkar, Chhaya Shinde
Department of Ophthalmology, Lokmanya Tilak Municipal Medical College and General Hospital, Mumbai, Maharashtra, India

Address for correspondence: Dr. Amol Ganvir, Shankar Nagar, Takiya Ward, Behind Laksh Hospital, Bhandara - 441 904, Maharashtra, India.
E-mail: amolganvir@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Ganvir A, Surendran AV, Shirwadkar S, Shinde C. Bilateral persistent pupillary iris membrane mimicking chronic anterior uveitis. Kerala J Ophthalmol 2023;35:226-7.

© 2023 Kerala Journal of Ophthalmology | Published by Wolters Kluwer - Medknow

TYPES OF PERSISTENT PUPILLARY IRIS MEMBRANE (PPIM)

It is categorized into type PPIM 1,2,3.[1]

Type 1: membranes involving the iris.

Type 2: membranes involving the iris and anterior capsule of the lens.

Type 3: membranes involving the iris, anterior capsule of the lens, and cornea.

PATHOPHYSIOLOGY

Iris tissue develops from the anterior extension part of the optic cup (mesodermal tissue).[2] Blood vessels usually enter the iris around the seventh month, and the tunica vasculosa lentis (TVL) disappears around the ninth month.[3] The pupillary membrane contains vessels and mesenchyme ventral to the lens. Posterior hyaloid vessels connect anteriorly to a network of vessels in the pupillary membrane, which regresses further. Incomplete resolution of the anterior TVL leads to a persistent pupillary membrane.[4]

CLINICAL MANIFESTATION

Usually, the patient remains asymptomatic. Membrane adhesion to the central part of the anterior lens capsule can cause impaired vision.

INVESTIGATIONS

Ultrasound biomicroscopy can give information about subtle iridolenticular adhesion.

OCULAR ASSOCIATION

- Persistent pupillary membrane is associated with stimulus deprivation amblyopia and anterior polar cataract.[5]

DIFFERENTIAL DIAGNOSIS

1) Posterior synechiae (chronic anterior uveitis)
2) Iridocorneal endothelial syndrome
3) Axenfeld–Rieger syndrome.

TREATMENT

a) Conservative treatment with or without mydriatic
b) Pharmacological mydriasis, occlusion therapy in the case of amblyopia
c) Surgical excision of an extensive and thick iris membrane obscuring the visual axis[6]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Duke-Elder S. Persistent Pupillary Membrane, Congenital Deformities. Vol 3. Part 2. Henry Kimpton: London; 1964. p. 775.
2. Mukherjee PK. Pediatric Ophthalmology. Daryaganj(New Delhi): New Age International; 2005.
3. Ko MK, Chi JG, Chang BL. Hyaloid vascular pattern in the human fetus. J Pediatr Ophthalmol Strabismus 1985;22:188-93.
4. Kraus CL, Lueder GT. Clinical characteristics and surgical approach to visually significant persistent pupillary membranes. J AAPOS 2014;18:596-9.
5. Mikhail M, Modabber M, Khan A. Surgical management of anterior capsular plaque associated with persistent pupillary membranes. Eye 2016;30:1274-5.
6. Oner A, Ilhan O, Dogan H. Bilateral extensive persistent pupillary membranes. J Pediatr Ophthalmol Strabismus 2007;44:57.

Comprehending Kaplan–Meier curve

Studies comparing survival rates between two groups of various interventions, such as surgical procedures or medications, are known as "survival analysis studies." These studies track the survival time or serial time, the interval between the time of entry to the study and the event of interest, which could be a death, the onset of a disease, or the appearance of a side effect.

The problem with these types of data is that all of the study subjects enrolled may not experience the event of interest. Some may not develop the disease during the entire study period, and some may leave the study for many reasons. These observations are called censored observations.

Broadly censoring can be divided into point censoring and interval censoring.[1]

Point censoring

It can be right or left censoring.

Right censoring includes those who did not experience the outcome of interest during the entire study period. In Figure 1, three double red line data do not need censoring as the event occurred during the study period. Blue dot lines are right censored as the first one left the study for some reason, and the second one did not develop the outcome during the entire study duration.

Left censoring (light blue interrupted lines) includes those who had the outcome of interest before enrolling in the study, and the onset time is unknown.

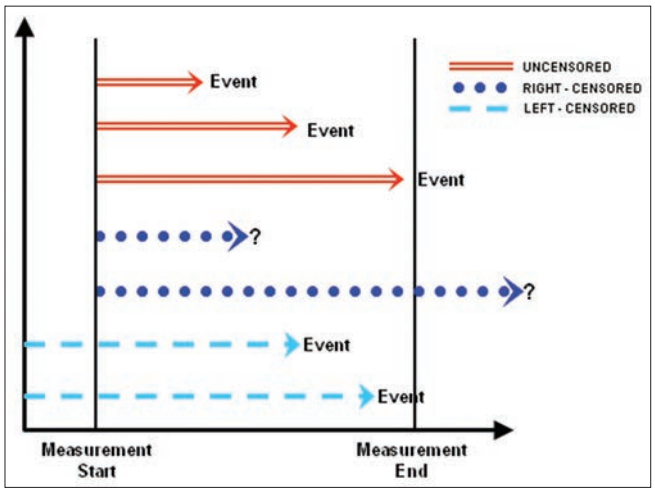


Figure 1: Different types of censoring

Interval censoring

This includes those with no disease or outcome at the beginning of the study, but later on, they developed the outcome of interest, but the exact onset time is unknown.

Survival analysis techniques used for dealing with censored data can be broadly classified into nonparametric (Kaplan–Meier product limit method), parametric (Weibull and exponential methods), and semiparametric method (Cox-proportional hazards method).[2]

Kaplan–Meier survival analysis is a nonparametric test and is predicated on three assumptions.[3]

1. We make the assumption that patients who are censored at any given moment have the same chances of survival as those who are still being monitored.
2. We assume that participants enrolled both early and late in the research have equal chances of surviving.
3. We presumptively believe that the event takes place at the time stated.

The data is represented as a curve. The X-axis denotes time in years or months, and Y axis denotes the cumulative survival. The curve has horizontal and vertical lines. The dimension of horizontal lines (parallel to the X-axis axis) corresponds to the duration of the interval between consecutive events, whereas the vertical distances represent the change in cumulative survival.

Median survival time is the time point at which the cumulative survival is 50%. Here in this graph the median survival time is 250 days. This can be used to compare between two groups. This is done by drawing a vertical line from where the curve crosses the 50% down to the time axis[4] [Figure 2].

Curves with many small steps usually have a higher number of participating subjects, whereas curves with large steps usually have a limited number of subjects and are thus as accurate [Figures 3 and 4].

Building a table with the three essential input components using an Excel spreadsheet or Word document is the first step in preparing for Kaplan–Meier analysis.[4] These are:

© 2023 Kerala Journal of Ophthalmology | Published by Wolters Kluwer - Medknow

1. Serial time
2. Status at serial time (1 = event of interest; 0 = censored)
3. Group (group 1 or 2, etc.).

The table is then arranged in ascending order of the serial time in each group [Table 1].

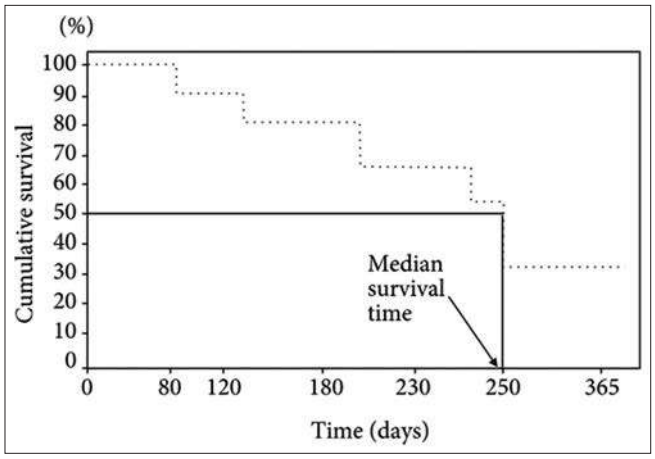


Figure 2: Kaplan–Meier curve denoting the median survival time

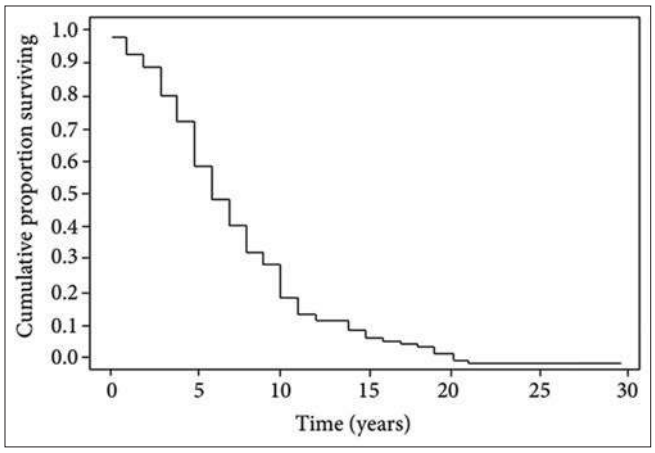


Figure 3: KM curve with multiple steps indicating more participants

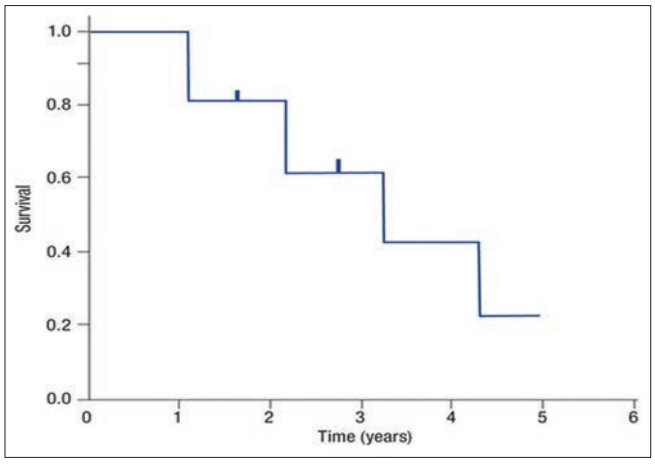


Figure 4: KM curve with large and few steps indicating less participants

Then Kaplan–Meier analysis is conducted using statistical software like SPSS.

There can be two or more curves depending on the number of study groups.

In clinical trials, comparing survival curves is of special relevance. The difference between the two survival curves can be easily seen, but the difference must be quantified to determine statistical significance. This can be done using a log-rank test or a Hazard ratio. Chi-square from the log-rank test will suggest whether the two curves are statistically different. The Cox-proportional hazards will show the increased event rate in one curve versus the other.

Furthermore, survival at various time points can be obtained and compared between curves. The survival curves in studies frequently have 2- or 5-year survival percentages. The median survivals for each curve can be simply compared if both cross through the 50 percentile point.[5]

CONCLUSION

The Kaplan–Meier method is a clever method of statistical treatment of survival times which not only makes proper allowances for those observations that are censored but also makes use of the information from these subjects up to the time when they are censored. It is possible to compare more survival curves (stratified by any factor) using a variety of techniques, including the log-rank test, Weibull and exponential approaches, and the Cox-proportional hazards method. The Kaplan–Meier analysis does not allow for confounder adjustment. It is, therefore, suitable for use in randomized clinical trials. In observational studies designed to test causal-effect relationships, it should only be regarded as a first-level analysis.

Table 1: Given in image provided in editable format

Subject	Serial time in years	Status at serial time (1=Event, 0=Censored)	Group 1 or 2
B	1	1	1
E	2	1	1
F	3	1	1
A	4	1	1
D	4.5	1	1
C	5	0	1
U	0.5	1	2
Z	0.75	1	2
W	1	1	2
V	1.5	0	2
X	2	1	2
Y	3.5	1	2

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Sandhya Somasundaran

Department of Ophthalmology, Govt. Medical College Kozhikode, Kozhikode, Kerala, India

Address for correspondence: Dr. Sandhya Somasundaran, Department of Ophthalmology, Govt. Medical College Kozhikode, Kozhikode, Kerala, India.
E-mail: drsandhyaraju1980@gmail.com

REFERENCES

1. Prinja S, Gupta N, Verma R. Censoring in clinical trials: Review of survival analysis techniques. Indian J Community Med 2010;35:217-21.
2. D'Arrigo G, Leonardis D, Abd ElHafeez S, Fusaro M, Tripepi G, Roumeliotis S. Methods to analyse time-to-event data: The Kaplan-Meier survival curve. Oxid Med Cell Longev 2021;2021:2290120.
3. Goel MK, Khanna P, Kishore J. Understanding survival analysis: Kaplan-Meier estimate. Int J Ayurveda Res 2010;1:274-8.
4. Rich JT, Neely JG, Paniello RC, Voelker CC, Nussenbaum B, Wang EW. A practical guide to understanding Kaplan-Meier curves. Otolaryngol Head Neck Surg 2010;143:331-6.
5. Sedgwick P, Joekes K. Kaplan-Meier survival curves: Interpretation and communication of risk. BMJ 2013;347:f7118.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Submitted: 14-Jul-2023 **Revised:** 16-Jul-2023
Accepted: 17-Jul-2023 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	**Quick Response Code**
DOI: 10.4103/kjo.kjo_91_23	

How to cite this article: Somasundaran S. Comprehending Kaplan–Meier curve. Kerala J Ophthalmol 2023;35:228-30.

Changing trends in the use of anti-vascular endothelial growth factor (anti-VEGF) biosimilars: Insights from the Vitreoretinal Society of India Biosimilars of Anti-VEGF Survey

Jay U Sheth, Michael W Stewart, Manoj Khatri, Shashank R Gupta, Shobhit Chawla, Anand Rajendran, Raja Narayanan, Indian J Ophthalmology 2021;69:352-6.

The subject of this article is to review the literature on "Changing trends in the use of anti-vascular endothelial growth factor (anti-VEGF) biosimilars: insights from the Vitreoretinal Society of India Biosimilars of Anti-VEGF Survey." Anti-VEGF drugs (Food and Drug Administration [FDA] approved ranibizumab, aflibercept, and brolucizumab, as well as off-label bevacizumab) are being widely used in the treatment of a variety of vitreoretinal vascular diseases like diabetic retinopathy, age-related macular degeneration, retinal vein occlusions, and others. India has an enormous market for biologics, which is the third highest in the Asia-Pacific region. The need for repeated injections over many years increases the cumulative cost of the treatment, which shifts the physicians' trend toward the less-expensive biosimilar drugs. Biosimilars (Razumab- ranibizumab biosimilar) are produced with reverse engineering techniques in living cell lines, with safety, efficacy, structure, pharmacodynamics, and pharmacokinetics that resemble approved biologics.

The study concluded that Indian vitreoretinal specialists are familiar with anti-VEGF biosimilars and there is a progressive trend favoring ranibizumab biosimilar over bevacizumab biosimilar. It also concluded that one-third of the participants deem the current price of ranibizumab biosimilar as appropriate to replace Avastin. In addition, enhanced pharmacovigilance and larger clinical trials are warranted before regulatory approval of these agents.

Objective of the study

The study objective was to present the changing trends in the use of anti-VEGF biosimilars among the members of Vitreoretinal Society of India (VRSI) and their perception regarding the safety, efficacy, pricing, and need for enhanced clinical trials before regulatory approval of anti-VEGF biosimilars.

Study design

It was a descriptive study in which an online survey among the members of VRSI was conducted in July 2018 and January 2020. Online surveys are cost-effective, time saving, and can collect both qualitative and quantitative data. They enable access to large and geographically distributed populations, and their results are similar to paper-based survey results. But the disadvantage is that many people may not consider them as significant, and hence, sometimes, the actual purpose may not be served.

Study setting

All the members of VRSI all over India were included, but we cannot make out if the regional differences would affect the results of the study.

Study population

The survey included both regular (all ophthalmologists with documented fellowship training in the field of retina and vitreous residing in India) and associate life members (all ophthalmologists with secondary interest in the field of retina vitreous) of VRSI. Exclusion criteria were not mentioned.

Sample size

Sample size was not calculated. Hence, we are not sure if the minimum sample size for the survey has been attained or not. The response rate was very low, that is, only 16% in 2018 (112 out of 700) and 12% in 2020 (98 out of 826). It would affect generalizability of the study, and it may not reflect what it was intended to do.

METHODOLOGY

Electronic surveys (as emails) were sent to members of the VRSI in July 2018 and January 2020, and recipients were asked to complete the online survey within 15 days.

Study tool

A questionnaire (kept as annexure) containing 12 questions was sent as Google Forms. It had a user-friendly design and layout. Well-designed questionnaires improve the reliability and validity of the collected data. No questions regarding the general characteristics of the study population like the

age, gender, and years of practice were included. It was not mentioned whether multiple responses from the same device were avoided.

Study variables

Qualitative variables assessed were participants' perceptions of efficacy, safety, pricing (Indian rupee [INR]), and the need for more clinical trials.

Data entry and analysis

Results were presented in the form of descriptive statistics. Even though frequency tables and doughnut charts were mentioned, they were not found. Most responses were reported as nominal data, whereas the question on appropriate pricing of Razumab was reported as ordinal data. Data were analyzed using Excel (Microsoft, Richmond, VA, USA) and STATA 16.1 (STATA Corp, LLC, College Station, TX, USA). Comparisons of 2018 and 2020 data were performed using the Chi-square test. Variables with P value <0.05 were considered as statistically significant.

RESULTS

Comparison of 2018 and 2020 surveys:

1. Awareness of anti-VEGF biosimilars increased from 96% to 100% ($P = 0.9$).
2. Percentage of respondents who wanted the approval of biosimilars to be given only after the completion of stringent clinical trials increased from 89% to 91% ($P = 0.93$).
3. Choice of anti-VEGF biosimilars: Usage of ranibizumab biosimilar increased from 41% to 56% ($P = 0.2$), and usage of bevacizumab biosimilar decreased from 9% to 2% ($P = 0.04$).
4. Continuing usage of biosimilars in the future: Though the authors said that the participants are more likely to use a ranibizumab biosimilar (increased from 73% to 82%) compared to a bevacizumab biosimilar (decreased from 7% to 6%), this result cannot be obtained from the study as the corresponding question did not compare the two biosimilars.
5. Participants' perception regarding safety and efficacy of anti-VEGF biosimilars: The proportion of participants who were satisfied with the safety of ranibizumab biosimilar increased from 61% to 68% in ($P = 0.59$), whereas the proportion of those satisfied with the safety of the bevacizumab biosimilar decreased from 30% to 25% ($P = 0.54$). Regarding the efficacy of the ranibizumab biosimilar, the percentage increased from 65% to 81% ($P = 0.32$) and that of the bevacizumab biosimilar did not change (from 29% to 30%, $P = 0.99$).
6. Economics of anti-VEGF biosimilars: Majority of the respondents believed that biosimilars have made anti-VEGF treatment more affordable (92% in 2020 and 83% in 2018, $P = 0.62$). When asked if the price of ranibizumab biosimilar (Razumab) was sufficient to switch from Avastin, the authors claim that similar proportions of respondents from 2020 (40%) and 2018 (37%) ($P = 0.82$) were in favor, but majority gave a negative response; but whether it is higher or lower than the present price of Razumab could not be analyzed from the graph. The participants were asked to estimate the price of ranibizumab biosimilar that would convince them to switch from Avastin. In 2018, the surveyed participants selected the switching price as $54 (42%), followed by $80 (23%), $74 (21%), and $94 (14%); in 2020, a plurality of participants also chose $54 (33%), fewer chose $74 (15%), but more number of participants chose $80 (29%) and $94 (23%).

DISCUSSION

The authors concluded that there was a significant increase in the use of ranibizumab biosimilar, whereas the use of bevacizumab biosimilar decreased. The results were not statistically significant, but clinically significant. The validation of biosimilars for unrestricted clinical use may require additional studies. Better designed clinical trials should be performed before biosimilars are approved. In 2020, physicians became more satisfied with the safety and efficacy of Razumab compared to 2018 and less satisfied with the safety of bevacizumab biosimilar. Regarding the future use of biosimilars, they anticipated using more of ranibizumab biosimilar. But no such data could be obtained from the questionnaire. The authors claim that despite episodes of Razumab-related sterile endophthalmitis, there is a trend among retina specialists in India to increasingly use this drug in their practice; but no questions regarding the awareness of complications of biosimilars among the participants were given in the questionnaire.

The general characteristics of the study group should have been included. The two groups should have been made comparable. Measures should have been taken to increase the response rate to improve the generalizability of the study.

CONCLUSION

This study represents the only survey data on physicians' perceptions of anti-VEGF biosimilars in India. Hence, a comparison is not possible and we do not know if the values obtained in the survey are similar. The 2-year interval between surveys both validates the original survey data and identifies trends, but the study does not have data regarding

the number of respondents in the 2020 survey who were also part of the 2018 survey cohort. Hence, we cannot comment on the generalizability and extended validity of the study. Physicians are well aware of biosimilars. There is an increasing trend toward prescribing a ranibizumab biosimilar. Physicians are generally satisfied with the safety and efficacy of biosimilars, but more rigorous trials should be conducted before regulatory approval. A further price reduction would be necessary for ranibizumab biosimilar to become the drug of first choice.

Acknowledgement

I would like to thank Dr. Carol Pinheiro, Assistant Professor in Community Medicine, Govt. TD Medical College Alappuzha, for her insight and expertise that assisted me in completing this article.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Dhanya Radhamani Sasidharan

Department of Ophthalmology, Govt. T D Medical College
Alappuzha, Kerala, India

Address for correspondence: Dr. Dhanya Radhamani Sasidharan, 'Souparnika', Kilikollur P O, Ayathil, Kollam, Kerala - 691 004, India.
E-mail: drdhanyars@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Submitted: 19-Sep-2022 **Accepted:** 06-Nov-2022 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	**Quick Response Code**
DOI: 10.4103/kjo.kjo_102_22	

How to cite this article: Sasidharan DR. Changing trends in the use of anti-vascular endothelial growth factor (anti-VEGF) biosimilars: Insights from the Vitreoretinal Society of India Biosimilars of Anti-VEGF Survey. Kerala J Ophthalmol 2023;35:231-3.

© 2023 Kerala Journal of Ophthalmology | Published by Wolters Kluwer -Medknow

Comments on "Amblyopia: Effectiveness of visual screening for early detection in a comparative study between urban and rural children"

Dear Editor,

I write this letter to express my views regarding an original article titled "Amblyopia: Effectiveness of visual screening for early detection in a comparative study between urban and rural children" which was published in the Kerala Journal of Ophthalmology January–April 2023 (Volume 35, Issue 1).

In our center during my pediatric ophthalmology posting, I observed that due to a mere lack of awareness and timely interference many children suffer from amblyopia, which is really disheartening. In such a scenario, the article helped me to know the prevalence of different types of amblyopia in rural and urban areas and the effectiveness of routine visual screening in school children. The article brought out the fact that screening programs can improve the quality of life of our budding generation and rural areas should receive more attention compared to urban areas.

I would also like to opine on certain aspects of the article which could have been looked into and included in the study.

1) The title of this study does not mention the age group of the study population, place of study, and the period of the study, hence appears incomplete.
2) The visual assessment was done using different methods which could have been standardized by using an objective method like cycloplegic refraction.
3) The study excluded mentally challenged children, but the prevalence of amblyopia is equally high among them.
4) Children with visual disturbance due to organic causes were excluded, but some degree of the amblyopic component can be present associated with such diseases.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Radhika Krishnan RB

Senior Resident, Regional Institute of Ophthalmology, Trivandrum, Kerala, India

Address for correspondence: Dr. Radhika Krishnan RB, Department of Ophthalmology, Regional Institute of Ophthalmology, Trivandrum, Kerala, India.
E-mail: rkrb1781993@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Submitted: 02-Jun-2023 **Accepted:** 03-Jun-2023 **Published:** 18-Aug-2023

Access this article online	
Website: www.kjophthal.com	Quick Response Code
DOI: 10.4103/kjo.kjo_64_23	

How to cite this article: Krishnan RB. Comments on "Amblyopia: Effectiveness of visual screening for early detection in a comparative study between urban and rural children". Kerala J Ophthalmol 2023;35:234.

© 2023 Kerala Journal of Ophthalmology | Published by Wolters Kluwer - Medknow

The reference trifocal IOL:
Providing maximum spectacle independence.

ZEISS

Seeing beyond



ZEISS AT LISA tri family

- Performance proven in more than 75 peer-reviewed publications
- Repeatedly reaching highest patient satisfaction
- Pupil independent design for full spectacle independence in all light conditions



zeiss.com/at-lisa-tri-family

Editor Dr. Smita Narayanan. Printed and published by Wolters Kluwer India Private Limited, on behalf of Kerala Society of Ophthalmic Surgeons. Printed at Nikeda Art Printers Pvt Ltd., Bhandup (W), Mumbai, India and published by Wolters Kluwer India Private Limited from A-202, 2nd Floor, The Qube, C.T.S. No.1498A/2 Village Marol, Andheri (East), Mumbai - 400 059, India.