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Cover Story: OGUCHI DISEASE

Fundus montage image of a 19 year old male showing Golden Tapetal reflex in both eyes.

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Contents

Editorial

Original research or research waste?
V. Sudha 107

Guest Editorial

Eye care in India– past, present, and future
Cherungottil Viswanathan Nair Radhadevi 109

Perspectives

Retinopathy of prematurity: Current status, treatment, prevention, and future directions from the perspective of developing countries
Eduardo Camacho-Martinez, Karla Torres-Navarro, Mayra Narvaez-Albarracin, Iryna M. Kuzhda, Marco Antonio Ramirez-Ortiz 112

Optha Insta

Acute traumatic maculopathy
Shruthy Vaishali Ramesh, Prasanna Venkatesh Ramesh, Meena Kumari Ramesh, Ramesh Rajasekaran 123

Major Review

Designing clinical trials
Smita Narayan 126

Retinal manifestations of COVID-19 disease - A review of available information
Kaberi Biswas Feroze 132

Research Methodology

Design and development of objective questionnaires
Praveen K. Nirmalan 139

Original Articles

Clinical profile and outcomes of ophthalmia nodosa in South India: A retrospective study
Kanika Chhabra, Pankaja Dhoble, Vaibhav Khanna 142

Prevalence of subclinical keratoconus in children presenting with refractive errors: A cross-sectional study
Rani Menon, Sharika Menon, Thekkuttuparambil Ananthanarayanan Ajith 146

Visual rehabilitation in pediatric cataract with primary intraocular lens implantation
Pradeep Ramteke, Dhaivat Shah, Hardik Jain, Garima Vaishnav, Rahul Singh, Amit Neema, Rajesh Vasure 151

Effect of position on the safety and efficacy of neodymium-doped: Yttrium aluminium garnet laser peripheral iridotomy in patients with primary angle-closure disease
Anitha S. Maiya 155

Ocular biometric parameters of children with refractive errors in the age group of 6–15 years
P. Thanusree, V. Mallika, Suma Unnikrishnan 160

Relationship among standard vision tests, quality of life, and ability to do daily activities in patients with glaucoma
Neethu Pradeep, Smita Narayan, N. Sujatha, Sinumol Thulaseedharan, V. Sudha 167

Comparison of applanation ultrasound biometry with optical biometry for intraocular lens power estimation in cataract surgery and their impact on prediction error
Merine Paul 173

Evaluation of retinal changes in normal pregnancy and gestational hypertension – A spectral domain optical coherence tomography based study
Niya Babu, Anthrayos C. V. Kakkanatt, Bindu Menon, Anchitha Meenu Rajeev 179

Awareness of retinopathy of prematurity screening among healthcare professionals in Palakkad district of Kerala
V. K. P. Geetha, Jayaraman Thrikkovil Pisharam, Parag K. Shah 185

Surgical Corner

A new technique of phacoemulsification without hydroprocedures
Narayan Bardoloi, Sandip Sarkar 189

Case Reports

Bilateral vitreous hemorrhage with branch retinal vein occlusion secondary to hyperhomocysteinemia: A rare case report
Amit Kumar Deb, Nithya Rathinam, Sandip Sarkar, Sangaraju Suneel, MalvikaMani, Subashini Kaliaperumal 194

Solitary eccrine spiradenoma of caruncle: A rare occurrence
Ankita Patil, Shahnawaz Kazi 197

A descriptive presentation of a family showing various features of aniridia and its genetic analysis
Meenakshi Wadhwani, Manoj Kumar, Rima Dada 201

Challenges in the diagnosis of early endogenous fungal endophthalmitis
Nusrath Parambil, Sheena Liz Mani, Anabi Shahi, Revati Ramesh 205

Complete eyelid loss due to dog bite: A rare presentation
Vinisha Dhawade Naik, Ugam P. S. Usgaonkar, Akshaya Nagvenker 209

Pseudoxanthoma elasticum: Pathognomonic ocular and skin lesions with histopathological confirmation
M. Manjunatha, Jayant Kumar, Amit Kumar Deb, Shanthi Radhakrishnan 211

Photo Essay

Fundus fluorescein angiography and optical coherence tomographic characteristics in acute multiple evanescent white dot syndrome
Priya Rasipuram Chandrasekaran 214

Innovations

Smartphone microscope in eye clinic to visualize fungus and Demodex
Pawan Prasher, Brahmjot Singh, Vipan K. Vig, John Davis Akkara 217

History Corner

The Ophthalmologist who won the Nobel Prize and declined one too
C. Biju John 222

Journal Review

T. U. Laly 226

PG Corner

Post trabeculectomy situations: Hypotony
Priyanka Sudhakar, Meena G. Menon 230

Letters to the Editor

Integration of research with clinical skills for house surgeons
Nandini Varma 236

Research in ophthalmology
Iodine Reghunadhan 238

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Original research or research waste?

"Skepticism is in the nature of science"

The COVID pandemic has spewed a torrent of research on its varied manifestations, detection techniques, treatment protocols, and its dreaded complications. Due to the urgency of information, many papers were released in the preprint stages itself and some prominent ones were later retracted due to the lack of rigor in analysis or because the data set could not be independently verified, as pointed out by scientists from the world over.[1] This constitutes not just a problem for the integrity of science and medicine, it is problematic for the notion of clinical trials and evidence generation, and definitely a black mark for the journals involved.

RESEARCH CAN BOTH COMMUNICATE AND MISCOMMUNICATE

Useful research is more likely to make a good difference to our knowledge. However, in most cases, the usefulness of an article can be ascertained only after its publication. For example, presently, there are an increasing number of published case reports regarding post-COVID patients affected with ocular opportunistic infections, vascular occlusions, and other issues.[2-5] But are these infections really in excess among the COVID-treated patients as compared to other patients who experienced similar hospitalization? Can we attribute these to the cytokine storm or autoimmune attributes of the disease or to the treatment protocols? Or are they only an apparent increase because of better reporting of COVID symptomatology? Equally problematic is the attributing of rare complications to COVID-19 vaccines. Raging controversies exist on the true incidence of these and whether they can be considered evidence enough to declare the particular vaccine unsuitable for use.

WHAT CONSTITUTES EVIDENCE?

Scientific evidence is a set of observations or results, which support or refute a hypothesis. Interpretation of the results is an important step and should be done in a scientific manner. The author has to defend his findings against all arguments from his peers and prove beyond doubt that no other explanations can give the same results. The evidence and the ways of making it are often closely scrutinized. A factual claim on the basis of personal observation collected in a casual manner is only anecdotal evidence and needs to be further analyzed. Thus, case reports should be interpreted not as evidence in a study of a disease but only as pointers to the need for further higher level analytical studies such as cohort studies and randomized controlled trials.

BUT DO TRIALS TELL THE WHOLE STORY?

There are numerous research trials occurring all over the world. Many of them do not get published. Out of those which do, how strong should we consider their results? Studies of published trial reports showed that the poor description of interventions meant that 40%–89% were nonreplicable; comparisons of protocols with publications showed that most studies had at least one primary outcome changed, introduced, or omitted; and investigators of new trials rarely did a systematic review of existing literature, and cited a very small and biased selection of previous relevant trials.[6] Although best documented in reports of controlled trials, inadequate reporting occurs in all types of studies – animal and other preclinical studies, diagnostic studies, epidemiological studies, clinical prediction research, surveys, and qualitative studies.

RESEARCH WASTE

Hence, the quality of information provided in published articles is variable and often incomplete. Inaccessibility of complete data is another common problem. This introduces bias, and has a detrimental impact on patient care and research. And such incomplete studies constitute research waste due to poor quality. Availability of full information on study methods facilitates critical appraisal, interpretation of study results, and appropriate replication. Proper reporting of results can improve clinical practice and policy, prevent unnecessary duplication, and help to inform ongoing and future research.[7] Because the original article with clinical implications can create an enduring impression by their conclusions, writing the reports requires great care, and careful peer review and critical analysis is a must.

THE ROLE OF JOURNALS

Journal publication is traditionally the primary means of communicating research results to the scientific community.

So by what criteria should a journal judge the quality of a submitted research paper? One of the important ways to look at it is that a good and useful work is "stable," i.e., not likely to be soon contradicted.[8] A stable interpretation is one which has a satisfactory answer to the question, "Why this interpretation rather than another?" Are there more likely, almost or equally as likely, or other possible explanations (including methodological error in the work in question)?

Selection biases shown by journals can be a major cause of skewed information. It has been found that clinical trials with positive results appear in journals about 1 year earlier than nonpositive trials.[9] New interventions will be accepted as effective, even though contrary evidence may already have been gathered but not yet published. And policy and treatment guidelines based on these new interventions will take priority.

Thus, the "burden of proof" lies on the researcher to show irrefutable evidence of his conclusions to his peers before and after publication. Published literature needs corroboration and repeatability, time and again. And journals with their team of editors and reviewers, as gatekeepers to this valuable evidence-based information, have a great responsibility to upkeep.

There are no shortcuts to good evidence. Are we equipped for it...?

V. Sudha

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Eye care in India– past, present, and future



THE LONG JOURNEY ... AND WHERE DO WE STAND NOW?

India has always had a long tradition of eye health care starting from the Vedic ages, 3000–1000 BC and transmitted through King Nimi, Sage Susrutha and Nagarjuna in the 2nd to 4th century AD and Vagbhata in the 6th century. Cataract surgery first done by Sage Susrutha[1]-couching-was done even in the early stages, but with below par conditions. Prescription of glasses was also done in those days. The "golden age" of Indian medicine was between 800 BC and 600 AD. With the arrival of Mughals by the 13th century, Unani medicine was introduced and Indian medicine was subdued for some time.

Western medicine was brought to India by the British in the early 18th century. Ayurvedic medicine was also revived during that time. Eye infirmary was started and the first medical school was established in Calcutta in 1822 which started functioning in1824. In 1747, French surgeon Jacques Daviel performed the first extracapsular cataract surgery, leading to notable advancement in cataract surgery. The 19th and 20th centuries saw tremendous progress in eye care leading to the modern era, including the introduction of phacoemulsification by Dr. Charles Kelmanin 1967. The great surge was seen with the starting of All India Institute of Ophthalmology and R *P* Centre for Ophthalmic Sciences, New Delhi in 1967, established by Princess Rajkumari Amrit Kaur. Eye institutes were started in other parts of India as well. Presently, well-equipped eye departments are there in all the medical colleges throughout the country, both in the government and private sector. Corporate hospitals with modern amenities and skilled staff have also come up in various parts of India.

India has always been in the forefront with regard to the prevention of blindness and eye care. The NPCB, launched in 1976 was directed toward prevention, treatment, and control of blindness. The District blindness control Society functioning in all the states conducted school health programs, cataract screening camps, and surgical camps. With the advent of new technologies, cataract surgery which was done at the campsite, was in due course shifted to the hospitals, to ascertain aseptic conditions. Vision 2020[2]- the right to sight was launched in 1999 by the World Health Organization (WHO) and the International Agency for the Prevention of Blindness to eliminate preventable blindness by 2020. This project also was carried out effectively in India.

With changing times, transition in health care has occurred both demographically and epidemiologically. The same changes reflect in the delivery of eye care as well. Subspecialties have been an inevitable change in the field of ophthalmology over the past few years. This has in turn brought us to crossroads with a shortage in the category of "the general or comprehensive ophthalmologist." In this scenario, we need to realign our resources to provide the best of comprehensive and specialty eye care to the public.

THE CONCEPT OF COMPREHENSIVE EYECARE

Comprehensive eye care (WHO)

Comprehensive eye care[3] is defined as the strategy which "aims to ensure that people have access to eye care services that meet their needs at every stage of life. This includes not only prevention and treatment services but also visual rehabilitation. Comprehensive eye care (CEC) also claims to address the full spectrum of eye diseases."

Being a person who has evolved through the times of "ab externo" incision cataract surgery to phacoemulsification, I am a strong supporter of technology and advances in ophthalmology. Albeit, we should not be oblivious of the fact that CEC is the face seen by the public and is the base of the eye care pyramid, without which we cannot effectively provide eye care to the masses.

Hence, the importance of the same cannot be left unseen.

The components of CEC are human resources, finance, health information, consumables and technology, and service delivery under governance to give a good quality high cover and safe health care. It should be incorporated into the health system and can be utilized for the care of chronic eye conditions-noncommunicable eye diseases, which may be quite challenging. The plan of action is based on a multilevel integrated structure which includes comprehensive eye examination, comprehensive eye care services, and comprehensive eye care system. The eye care delivery should be planned according to the disease, socioeconomic and demographic setting.

THE EYE CARE PYRAMID

The Eye Care Pyramid[3,4] is an infrastructure model for the implementation of VISION 2020: The right to sight. Eye care infrastructure consists of the primary, secondary, tertiary, and advanced tertiary centers.

Primary eye care Centre (PEC) is an integral part of comprehensive eye care. In the PEC, health education, identification of symptoms, recording basic eye examination, diagnosis, and timely referral are done. This forms the base of the eye care pyramid, along with community eye care.

Secondary centers provide quality eye care which includes diagnosis of eye diseases and high-quality surgery mainly for cataract, the leading cause of treatable blindness.

Tertiary centers provide comprehensive services and training of personnel. Specialized surgeries for glaucoma, retina, and cornea are done here. Training and Continuing Medical Education (CME) is also conducted.

Center for excellence caters to service delivery of complex eye diseases, training of trainers in subspecialties, vision rehabilitation, and supportive advice.

CEC can be carried out in medical colleges, district hospitals, and even in the private sector.

Education and research should be undertaken in such centers. School Heath programs and eye camps intensify the community eye care. CME along with training programs for internal and external faculty helps to keep pace with advancing technology and knowledge. This also helps to develop good rapport between the Ophthalmologists. Teamwork is important in cases such as trauma or diseases. A good teamwork with departments such as neurology, neurosurgery, ENT, Dental, or plastic surgery can be of great help in tackling complex cases.

General ophthalmologists can handle specialty cases with sufficient training.

Furthermore, specialists can do the work of a general Ophthalmologist, if he/she is willing. That depends largely on the attitude and skill of the specialist. Interaction between the general Ophthalmologist and specialist will be helpful in the delivery of eye care services, especially in chronic cases.

Teleophthalmology is becoming important as an effective eye care modality.[5] It can play an additional role in screening, emergency eye care, urgent diagnosis, treatment, and prompt referral. Useful in conditions such as diabetic retinopathy, retinopathy of prematurity, and glaucoma.

FUTURE OF EYE CARE IN INDIA

The way forward depends on certain factors-human resource development, skill-based training, appropriate eye care to all and interaction between eye care providers– both public and private sectors, usage of technology for documentation, data collection and analysis along with innovation, and translational research[6]

How can we go forward?

By strengthening the components of the health system, assuring eye health continuity and service delivery, integration into the healthcare system, use of modern technologies and data collection tools, training with regular maintenance, and by providing rehabilitation to the irreversible visually impaired.

In training centers, trainees or postgraduates should be exposed to handle all types of ophthalmic cases, so that when they go out, they will have no difficulty in giving good eye care service to patients. Now is the time to redefine eye healthcare delivery so that it is accessible to the masses without much difficulty.

There surely is a bright future for Indian Ophthalmology. The younger generation should be able to maintain and intensify the glory of Indian Ophthalmology, as there is neither scarcity of talent or shortage of patients.

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Retinopathy of prematurity: Current status, treatment, prevention, and future directions from the perspective of developing countries

ABSTRACT

Retinopathy of prematurity (ROP) is the leading cause of preventable blindness in pediatric population living in developing countries. Increasing survival rates of premature patients have been globally improving during the last years and this is the main reason of blindness rate escalation secondary to ROP. The advent of intravitreal injections of antiangiogenic agents in therapeutic ophthalmological arsenal has provided an easier and faster way to prevent retinal detachment in this extremely fragile population. In the nearest future, we will witness, how medical science will provide enough scientific evidence to treat properly these patients with the lowest and safest dose of anti-vascular endothelial growth factor intraocular injections with the fewer systemic side effects. Meanwhile, transpupillary retinal laser photocoagulation of the avascular retina will remain the "gold standard" for ROP treatment, and for sure, this option could also provide a feasible alternative in the future for those cases, where intravitreal injections will fail. Neonatologists and ophthalmologists should keep on working together to fight against children's blindness, synchronizing retinal examinations timing criteria by adequate eye screening. Low- and middle-income countries' health governmental care suppliers should organize suitable programs for providing adequate neonatal care for premature patients and preventing, detecting, and treating effectively ROP. Training and teaching ROP screening and treatment programs are also a responsibility to be taken by local health care authorities and university residency courses for young ophthalmologists. This review describes the situation, state-of-the-art treatment, blindness prevention options from developing countries' viewpoints.

Keywords: Blindness, prevention, retinopathy of prematurity, screening

RETINOPATHY OR PREMATURITY IN THE WORLD

Retinopathy of prematurity (ROP), a preventable complication of preterm birth, is an important cause of blindness worldwide. In 2010 alone, it is estimated that around 184,700 newborns presented some degree of ROP and that 20,000 of these became blind or severely visually impaired, and 12,300 developed mild/moderate visual impairment.[1] Regional rates of ROP vary, 50% of the countries with the most premature births are in Asia, and even in this continent, the difference in income between countries translates in a different prognosis for the patients.[2] To mention a few examples, India estimates that 10–20,000 of babies per year may need treatment,[3] compared to <350 per year in the UK.[4] In Mexico, reports

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vary from center to center from 4.7%[5] to 28.8%[6] of premature children requiring treatment.

NORMAL RETINAL VASCULAR DEVELOPMENT

The normal retinal vascular development begins at 15 weeks of gestation. The nasal ora Serrata is the first edge to be vascularized, between 34 and 36 weeks, the temporal side is vascularized from week 36 to 40.[7] This process is triggered in part by vascular endothelial growth factor (VEGF), an oxygen-regulated factor produced by astrocytes in the avascular retina in response to hypoxia,[8] and insulin-like growth factor-1 (IGF-1), a non-oxygen-dependent factor.[9] If an infant is born prematurely, this physiologic process is interrupted, and hence the retina is prone to develop ROP.

PATHOPHYSIOLOGY OF RETINOPATHY OF PREMATURITY

Since 1974, it has been known that oxygen plays an important role in the pathophysiology of ROP.[10] There are two known phases of ROP development. The first phase, which takes place between week 22 and 30 postconceptional age, consists of a delay in the physiologic development of retinal vasculature caused by high oxygen administration relative to intrauterine oxygen levels, which gives place to a peripheral avascular retina that has decreased production of VEGF and IGF-1 arresting retinal blood vessel growth.[11] The second phase, taking place between weeks 31 and 34, is characterized by disorganized vasoproliferation at the junction of the vascularized and avascular retina caused by abundant VEGF and IGF-1 secretion, with consequent intravitreal aberrant angiogenesis once oxygen supplementation is reduced.[12] High oxygen supply triggers vasoconstriction, vascular obliteration, peripheral ischemia, and the permanent interruption of retinal vascular formation and overproduction of VEGF which leads to neovascularization and its related complications.[12] A third phase has also been described, characterized by fibrovascular tractional detachments of the retina. This phase occurs when the aberrantly formed vessels interact with collagen and other vitreous components leading to progression of the disease despite inhibition of angiogenesis.[13]

It has been shown that the time of use and the O_2 concentration, regardless of the method of administration (endotracheal tube, mask, or continuous positive airway pressure machine), have a direct influence in the development and severity of ROP.[14] The Supplemental Therapeutic Oxygen for Prethreshold ROP trial attempted to find if supplemental oxygen could reduce the probability of progression from pre threshold to threshold ROP and the need for ablation treatment. Results showed that oxygen saturation levels of 96%–99% did not increase the severity of ROP in eyes with prethreshold ROP, and that ROP is not a reason to withhold oxygen supply for cardiopulmonary reasons.[15] Despite several other studies made on the role of oxygen and ROP, an ideal range of oxygen supplementation remains to be established; for a lower oxygen supplementation is associated with lower rates of ROP, but higher mortality.[16]

RISK FACTORS

Gestational age and birth weight

From the first randomized trials for ROP treatment, it has been known that gestational age (GA) and birth weight (BW) are the most important risk factors for the development of ROP. In the Cryotherapy for ROP Cooperative Group (CRYO-ROP) study, a BW ≤1251 g was associated with developing threshold ROP, and an increase of 100 g decreases the chances of developing ROP by 27%.[17] Since these findings, several studies have tried to find protective factors for ROP, but even recent trials have coincided in a larger BW and an older GA as protectors for the development of ROP.[18]

Pulmonary factors

Several pulmonary conditions have also been associated with the development of ROP. Patients with apnea of prematurity have a greater risk of ROP because they are more prone to require mechanical ventilation.[19] Respiratory distress syndrome, a condition characterized by surfactant deficiency in which the neonates may become hypoxic and require mechanical ventilation, is also a common predisposing factor.[20] Another condition associated with the development of ROP is bronchopulmonary dysplasia, which is characterized by oxygen dependence beyond 28 postnatal days, once again relating to the role of oxygen and pulmonary function in ROP.[21]

Intraventricular hemorrhage

This condition has several causes and has been reported to be present in around 25%–30% of all preterm infants <1500 g.[22] This complication of prematurity has been associated with ROP in several studies,[21,23] and in a Turkish study, it was associated with a greater risk of ROP.[19]

Infectious

Sepsis

Another of the most common risk factors associated with ROP and even with severe ROP in particular is neonatal sepsis. The Extremely Low GA Newborn study published a report on the relationship between bacteremia and ROP in 1059 infants born before week 28. Its findings were that late neonatal bacteremia is an independent risk factor for prethreshold/threshold ROP and plus disease, and presumed

late bacteremia seems to be related to prethreshold/threshold ROP.[24] The New York state study also reported neonatal sepsis associated with an elevated risk of ROP.[25]

Necrotizing enterocolitis

Necrotizing enterocolitis is a condition in which the intestines of the premature infants are inflamed, the immune response caused by this condition can extend to organs like the brain causing an increased risk for neurodevelopmental delay.[26] This life-threatening condition has also been identified as an independent risk factor for ROP in studies based in New York and Canada.[26,27]

CLASSIFICATION

International Classification Retinopathy of prematurity

To standardize the description of ROP findings and create a treatment consensus, the International Classification of ROP (ICROP) was created. It was first published in 1984 and has since been revised multiple times, the last of which was in 2005.[28] Since then, this classification has been used in the different publications regarding ROP.

Zones and stages of disease

The location of the retinopathy is described with 3 concentric zones centered on the optic disc. Zone 1, the innermost zone, has a radius extending twice the distance from the center of the optic disc to the center of the macula. Zone II extends from the edge of zone I to the nasal ora Serrata, and zone III is the residual crescent of retina anterior to zone II. The extent of disease is described with the number of hours of the clock or 30° sectors involved.

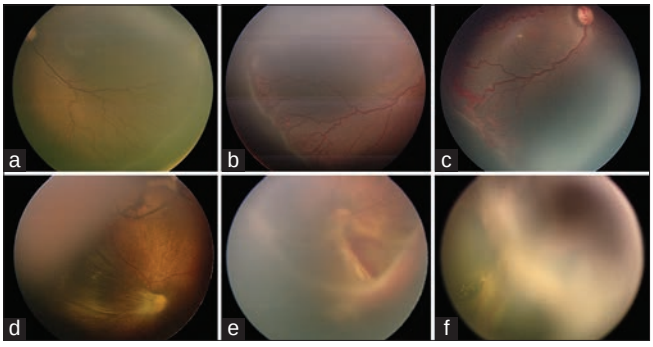


Figure 1: (a)Stage 1 consisting in demarcation line is seen as whitish line located between the normally vascularized retina and the peripheral avascular retina. This stage resolves spontaneously without progression. (b) Stage 2 consisting in visible ridge at demarcation line with height and width without blood vessel growth towards vitreous. This stage carefully requires only observation by trained ophthalmologist. (c) Stage 3 characterized by severely abnormal blood vessel growth toward the central vitreous; when this stage is associated with Plus Disease (enlarged and twisted blood vessels emerging from optic nerve) it can lead to retinal detachment so treatment with infrared laser photocoagulation (or Anti VEGF intraocular injections) should be performed within the next 48 hours after diagnosis is made. (d) Stage 4A Partially retinal detachment not involving foveal area. Vitreoretinal surgery or scleral buckling may be indicated. (e) Partially retinal detachment involving macular area. Vitreoretinal surgery may be indicated. 1F Total retinal detachment. Surgical treatment almost always does not provide any visual acuity improvement.

There are 5 stages of ROP increasing in severity from 1 to 5 [Figure 1(a-f)], and staging is determined by the most severe manifestation present in an eye. Stage 1 is characterized by a demarcation line separating avascular retina from vascularized retina. This stage resolves spontaneously without progression. Stage 2 is characterized by a ridge in the region of the demarcation line with height and width above the level of the retina. This stage carefully requires only observation by a trained ophthalmologist. Stage 3 presents extraretinal fibrovascular proliferation or neovascularization extending from the ridge into the vitreous; when this stage is associated with Plus Disease (enlarged and twisted blood vessels emerging from optic nerve) it can lead to retinal detachment so treatment with infrared laser photocoagulation (or Anti VEGF intraocular injections) should be performed within the next 48 h after diagnosis is made. Retinal detachment is the defining characteristic of Stage 4, and it is divided into extrafoveal (4A) and foveal (4B) involvement. Stage 5 is defined by a total retinal detachment, usually funnel-shaped. Surgical treatment almost always does not provide any visual acuity improvement.[28]

Plus disease

Additional characteristics indicating the severity of active ROP have been described. These findings include increased venous dilatation and arteriolar tortuosity of the posterior retinal vessels. If dilation and tortuosity are present in at least 2 quadrants, then plus disease is diagnosed.[28] Later stages include iris vascular engorgement, poor pupilar dilation, and vitreous haze.

Pre-plus disease is diagnosed when there are vascular abnormalities in the posterior pole but not fulfilling the criteria for plus disease.[28] The importance of this stage of disease is that the clinician should give close follow-up for it can progress to plus disease.

Aggressive posterior disease

Aggressive posterior ROP is a rapidly progressing form of ROP affecting zone I or II that if left untreated can progress to stage 5. This disease is characterized by increased dilation and tortuosity in all 4 quadrants out of proportion to the peripheral retinopathy [Figure 2]. This variant does not progress through the classic stages and can also present circumferential vessels at the edge of the vascularized retina.[28]

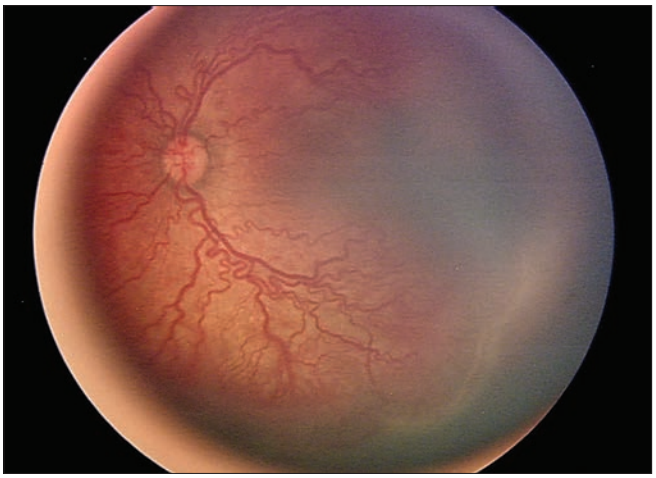


Figure 2: Aggressive posterior disease characterized by fast progression of flat neovascularization in Zone 1 with dilation and tortuosity in all 4 quadrants.

Type I and II retinopathy of prematurity

In other sections of this review, the treatment will be thoroughly discussed. However, speaking of classification and staging of ROP, a mention of type I and type II ROP is in place. The Early Treatment for ROP study's conclusions recommended treatment for patients having what they called Type I ROP, which includes any stage zone I ROP with plus disease, zone I stage 3 with or without plus disease or zone II stage 2 or 3 ROP with plus disease. Type II ROP includes zone I stage 1 or 2 without plus disease or zone II stage 3 without plus disease, and close observation is indicated in these patients.[29]

Upcoming new classification

Given the advances in neonatal care, anti-VEGF therapy, and imaging, the ICROP is undergoing an update that adapts to these advances. Among the changes that are under consideration is the inclusion of a new intermediate zone between zones I and II that will be known as posterior zone II, recognition that plus disease and pre-plus reflect a continuous spectrum of a vascular abnormality, definition of nomenclature representing ROP regression and its sequelae, definition of nomenclature regarding ROP reactivation after treatment, among others.[30] The intention of this new revision is to improve quality and standardization of ROP care worldwide.

SCREENING

When to perform screening

Since ROP is a disease that can lead to preventable blindness, screening should be done in all preterm infants at risk for developing the disease so that those requiring treatment can be detected in time. In the United States, screening is indicated in all infants with BW ≤1,500 g or GA ≤30 weeks. Infants weighting between 1500 and 2000 g or having a GA >30 weeks, but that had an unstable clinical course can also be examined for ROP. First examination should be performed between the 4th to 6th postnatal week or at 31 weeks post menstrual age, whichever is later.[31] The frequency of further examinations is determined by the funduscopic findings [Table 1],[32] with more severe disease needing a closer follow-up. Examinations can be stopped at post-menstrual age 50 if no prethreshold disease is present, or when vascularization of zone III is achieved, without previous zone I or II ROP, or if there is a complete regression of ROP.[32,33]

Table 1: Recommended intervals of follow-up eye examinations for retinopathy of prematurity screening

Retinal findings	Timing of eye examination
Immature vascularization in zone I or posterior zone II	1 week or less
Stage 1 or 2 ROP in zone I	
Stage 3 ROP in zone II	
Suspected or present aggressive posterior ROP	
Immature vascularization in posterior zone II	1-2 weeks
Stage 2 ROP in zone II	
Unequivocally regressing ROP in zone I	
Stage 1 ROP in zone II	2 weeks
Immature vascularization in zone II	
Unequivocally regressing ROP in zone II	
Stage 1 or 2 ROP in zone III	2-3 weeks
Regressing ROP in zone III	

ROP – Retinopathy of prematurity

Table 2: Comparison of the advantages of retinopathy of prematurity treatment with transpupillary laser photocoagulation and bevacizumab intravitreal injections

Laser photocoagulation	Anti-vascular endothelial grow factor
Gold standard	Less myopia
No systemic complications	Easier to perform
Shorter follow up	Short time treatment
Known long term functional results	Shorter exposure to anesthesia

How to perform retinopathy of prematurity screening

Screening of all infants at risk of ROP should be performed under pupillary dilation. Different drugs can be used to achieve dilation: 0.2% cyclopentolate and 1.0% phenylephrine solution, 1% tropicamide and 2.5% phenylephrine solution. Fundus examination should be thorough, with careful examination of the peripheral retina to be able to accurately classify the disease. Indirect ophthalmoscopy is the mainstay technique for examination. Eyelid speculum and indentation can be performed as needed [Figure 3]; however, indentation has been proved necessary to examine the inferior midperipheral retinal vasculature and the far peripheral temporal retina (Zone III).[34] It is advisable for a nurse with



Figure 3: Indirect ophthalmoscope retinal examination performed in a premature patient at risk of developing retinopathy of prematurity is examined at Neonatal Intensive Care Unit



Figure 4: Retcam 3 retinal imaging is performed by two trained ophthalmologists under the care of a pediatrician who is monitoring patient's temperature and vital signs during the whole procedure

experience in neonatal care or a neonatologist to assist during the examination to swaddle the infant and stabilize the head, as well as to intervene if the infant develops apnea or bradycardia during the examination.[35]

There is concern regarding ROP examination and the stress it causes the infant. Several studies have been made trying to find whether the use of topical anesthesia with proparacaine, oral dextrose, oral sucrose, breast milk, and use of pacifiers can be an effective analgesic, however, results have been contradictory or found that no significantly alleviate pain during the procedure.[36-38] There is also an ongoing study to determine which kind of speculum induces less pain in the neonate.[39] Portable retinal cameras have been shown to be a safe and feasible method to screen and document retinas of premature babies [Figure 4]. Evaluation using indirect ophthalmoscope with and without speculum, as well as with imaging such as RetCam 3 (Natus Medical Incorporated, Pleasanton CA) have also been compared to find the less stressful method of examination, finding that examination by indirect ophthalmoscopy without speculum is the less stressful method;[40] however, as mentioned before, in order to properly examine the whole retina speculum and indentation may be necessary.

TREATMENT

Ablation of avascular retina

In the late 1980s, the CRYO ROP trial, established the efficacy of cryotherapy to treat stage 3 ROP zone I or II with Plus disease in at least 5 consecutive or 8 cumulative clock hours (threshold ROP).[28,41] The results of this study demonstrated that the ablation of avascular retina resulted in nearly 50% reduction of unfavorable anatomic outcomes such as retinal detachment (21.8% in eyes treated with cryotherapy compared to 43% in control group) or macular dragging; also, they demonstrated that this treatment improved the functional outcomes when compared with the outcomes of control group, final visual acuity 20/200 or less in 44.7% versus 64.4% respectively.[42]

Disadvantages of cryotherapy included prolonged time of general anesthesia to complete the treatment and difficult application in the posterior zone that in some cases required conjunctival incisions. Later, in the 15 years' follow-up of the patients, there was a description of extensive retinochoroidal scars in the peripheral retina caused by the thermal ablation and increasing prevalence of high myopia.[43]

Since then, retinal ablation with laser photocoagulation has proven to be safe and at least as effective as cryotherapy to treat threshold ROP. Despite the reduction of rates of unfavorable outcomes, they are still high enough so that research for a new treatment with fewer complications and better results is still ongoing.

Results of Early Treatment for ROP (ETROP) demonstrated a reduction of unfavorable anatomic and functional results in ROP 1 which was defined as eyes with high risk of progression of ROP and loss of vision. Type I ROP includes any stage zone I ROP with plus disease, zone I stage 3 with or without plus disease or zone II stage 2 or 3 ROP with plus disease.

Type 2 ROP (eyes that did not meet the treatment criteria mentioned above) were evaluated every 7–10 days until spontaneous regression or progression to type 1 ROP occurred. These patients should be followed closely, until complete vascularization of zone III occurred.[44]



Figure 5: Type 1 retinopathy of prematurity undergoing transpupilar laser treatment under general anesthesia. This procedure should be performed on a nearly confluent pattern in the avascular retina.

The aim of laser treatment is the ablation of the entire avascular retina as rapidly and as completely as possible with minimum side effects. The most used laser is diode red (810 nm) with laser indirect ophthalmoscope. This treatment can be done either in the Neonatal Intensive Care Unit (NICU) OR in an Operating Room, under topical or general anesthesia. It is advisable to have a neonatologist or pediatric anesthesiologist in the same room to have adequate monitoring.

It is necessary to instill dilating drops twice, 1% tropicamide and 2.5% phenylephrine, at least 30 min before the treatment. A pediatric eye speculum, scleral depressor, or sterile cotton-tipped buds and tetracaine for topical anesthesia are also needed. It is also very important to ensure that the patient is warm throughout the procedure Figure 5. To achieve this, reducing the use of air conditioning, use of thermal mattress and avoiding excessive irrigation of eyes during treatment are advised, since it can cool the patient's head.[44]

Antiangiogenics

Laser photocoagulation is still the "gold standard" for the treatment of ROP, however, the use of intravitreal antiangiogenics in recent years has increased worldwide for the advantages of this kind of treatment over the retinal ablation. In certain clinical situations (poor pupillary dilatation secondary to rubeosis iridis, optic media not clear, haze vitreous and vitreous hemorrhage), the use of laser photocoagulation could be extremely difficult to perform, but an intravitreal injection of antiangiogenic would be easier and faster treatment [Table 2].

Another disadvantage of laser photocoagulation, especially in zone I cases and when near confluent laser therapy is performed, is that unavoidable consequences occur frequently, with clinical implications including loss of visual field, myopia, and development of late angle-closure glaucoma.[45-47]

Bevacizumab (Avastin; Genentech, South San Francisco, CA), is a recombinant humanized anti-VEGF antibody used to treat ROP since 2007. A prospective, stratified, randomized, controlled, multicenter, clinical trial, Bevacizumab Eliminates the Angiogenic Threat of ROP (BEAT-ROP) assessed the efficacy of intravitreous bevacizumab (IVB) monotherapy in the treatment of severe ROP in zone I or posterior zone II compared with conventional laser therapy and concluded that IVB showed significant benefit for zone I but not for zone II disease, as compared with zone II. BEAT-ROP study included 300 eyes with type 1 ROP apart from zone II stage 2+; they were randomized to the IVB (0.625 mg) group or to the conventional laser. They found that a dose of 0.625 mg of IVB can halt the progression of severe ROP, revert pathologic angiogenic changes, and induce the progression of physiologic intraretinal vasculature. The rate of recurrence of ROP was significantly lower in the antiangiogenic group versus laser photocoagulation (6% vs. 42%) and was diagnosed earlier in laser group 6.2 ± 5.7 weeks and 16.0 ± 4.6 weeks. There was no evidence of local or systemic toxicity.[48]

Ranibizumab (Lucentis, Novartis) is indicated for the treatment of ROP with zone I (stage 1+. 2+, 3 or 3+), zone II (stage 3+), or AP-ROP disease, making it the only FDA approved pharmacological therapy for this disease. The approval is based on the results of Ranibizumab versus laser therapy for the treatment of very low birthweight infants with ROP (RAINBOW) study. This was a randomized, open-label, multicenter trial that was done in 26 countries. 225 participants were randomly assigned to receive a single bilateral intravitreal dose of 0.2 mg ranibizumab, 0.1 mg ranibizumab or laser therapy. The 0.2 mg dose of ranibizumab might be superior to laser therapy, with fewer unfavorable ocular outcomes than laser therapy and with acceptable 24-week safety profile.[49]

Timing of the administration of IVB monotherapy is critical. It is an ideal treatment when ocular VEGF levels are high with neovascularization (phase 2).[11] It is not recommended in late stages (4b, 5) after the development of retinal detachment because it could accelerate the progression.[50]

VEGF is fundamental for the normal development of organs such as the brain, heart, kidneys, and retina. After intravitreal injection, bevacizumab is found in the systemic circulation and plasma VEGF levels decrease, so there are concerns

about possible adverse effects, especially concerning neurodevelopmental disability.[51] The current anti-VEGF intravitreal injections doses used for Type 1 ROP treatment and the lack of convincing association with neurodevelopment impairment[52] is not evidence of the lack of an association, especially because there are no adequately powered or controlled studies addressing this question.[53] Randomized clinical trials are required to better understand the systemic safety of intravitreal Bevacizumab in treating ROP. Finally, we suggest that until high quality evidence has been established, clinicians carefully should weigh the benefits and risks of IVB treatment before treating infants with ROP.

A much lower dose may be effective for ROP while reducing systemic risk. Wallace *et al*., investigated the efficacy of different doses of intravitreous bevacizumab in 59 infants with ROP type 1. The results suggest that 0.004 mg may be the lowest dose of bevacizumab effective for ROP, with 90% of cases having successful outcomes after 4 weeks of injection.[52]

The cases with recurrence of ROP are not uncommon, so the appropriate time to perform and to suspend follow-up examinations to allow timely diagnosis and treatment of recurrence after IVB monotherapy must be structured properly and extended until retinal vascularization is considered complete, which may not necessarily reach the ora Serrata in the most immature infants.The risk period of recurrence of ROP after IVB is predictable with a critical 10-week recurrence window from approximately 45–55 weeks after injection, with recurrence developing at mean of 51.2 weeks and infrequently, as late as 65 weeks. It could be a good practice to perform weekly examinations until 70 weeks after intravitreal of anti-VEGF.

The recurrence can be seen with indirect ophthalmoscopy, but it is best documented by fluorescein angiography, especially in late recurrences of ROP with anti-VEGF monotherapy.[53]

Some practitioners implement IVB as part of a dual therapy with laser, rather than as monotherapy; however, this combination may have undesired consequences. Laser may cause more recurrences because of breakdown of the blood-retinal barrier, perhaps allowing more escape of antiangiogenic from the eye to bloodstream.[54]

Insufficient data about the safety of intravitreal antiangiogenic agents precludes strong conclusions favoring routine use of these drugs. Further studies are needed to evaluate the effect of anti-VEGF agents on structural and functional outcomes in childhood and delayed systemic effects including adverse neurodevelopmental outcomes.[55]

One of the main disadvantages of performing laser is the need for general anesthesia, the FDA issued an alert in 2016 about the use of anesthetics in children under 3 years of age and with procedures >3 h, or repeated procedures, where exposure to anesthetics can interfere with the neurological development of the patient, especially susceptible for being in a very active phase of the development of the nervous system and its neuronal connections. The existing information is based on experimental studies and although there is insufficient clinical evidence to extrapolate the experimental results to humans, the problem must be considered in the therapeutic options.[56]

Despite proper screening and ablative treatment, it does not always prevent disease progression to retinal detachment. 12% of patients with type 1 ROP and ablative treatment will progress to stage 4 or 5 and will require surgical treatment.[46] The goal of surgery is to remove the scaffold for fibrovascular proliferation and remove excess of VEGF levels. New instruments in vitreoretinal surgery have made ROP surgery more feasible, with better anatomical results.[57] It has been observed that stage 4a surgery has better anatomical results with a greater probability of long-term visual function, in stage 4B these are acceptable anatomical results, but in stage 5 the anatomical and visual results are still unfavorable.[58]

Other treatments

Other therapies have been tried, the use of beta-adrenergic blocking agents, which modulate the vasoproliferative retinal process, may reduce the progression of ROP or even reverse established ROP, a meta-analysis of beta-blockers suggests that there is insufficient evidence to determine the efficacy and safety of this therapy in the prevention or reverse established ROP.[59]

Vitamin A as a preventive therapy for ROP, the extremely preterm infants are prone to vitamin A deficiency, Sun *et al*. conducted a prospective, randomized study in 262 extremely preterm infants to a vitamin A group versus a control group, with no adverse events, type 1 ROP occurred in 11 of 262 infants (4.2%), whereas 9 control patients (6.9%) required intervention compared with 2 patients (1.6%) from the vitamin A-supplemented group. The group of vitamin A had lower unadjusted rates of Type 1 ROP and bronchopulmonary dysplasia than the control group. This study demonstrated the vitamin A supplementation reduced the incidence of Type 1 ROP and may also have a positive impact on reducing bronchopulmonary dysplasia.[60] The administration of Vitamin E remains controversial in ROP, therefore, its prophylactic use in high doses is not recommended for premature patients.[61]

RECURRENCY TREATMENT

The reactivation of ROP in the BEAT-ROP study reported that the interval from initial treatment to treatment requiring recurrence was longer in the bevacizumab group compared with the laser group. This interval was approximately 3 months longer in zone 1 eyes.[50] Jennifer Hu made a report of late reactivation and progression of ROP after intravitreal bevacizumab, the mean time between initial treatment and retreatment-requiring recurrence was 14.4 weeks (4–35 weeks), no eye that received laser treatment for recurrence progressed to retinal detachment, therefore, in the case of recurrences, it is recommended to perform photocoagulation in the avascular area.[55] Risk factors for recurrence of type 1 ROP are extensive retinal neovascularization and oxygen requirement after intravitreal therapy.[62] Transient blockade of VEGF rather than the long-term downregulation induced by laser supports this therapeutic line in reactivation of ROP. The long interval to recurrence for patients with anti-VEGF therapy suggest that follow-up must be prolonged and highly vigilant.

SEQUELAE

The sequelae of ROP include refractive error, strabismus, cerebral impairment. Preterm birth affects normal development and function, the thickness at the fovea is increased and the foveal avascular zone is smaller in children born preterm than that of children born at term, regardless the presence of ROP.[63]

Among refractive problems, myopia is one of the most well-known ocular abnormalities associated with premature birth. Some studies have shown the prevalence of myopia correlates negatively with BW and GA, but positively with increasing severity of ROP. It could be secondary to arrested development of the anterior segment, a low axial length-to-power ratio, a shallow anterior chamber depth, a thicker lens, and a steeper corneal curvature.[64]

In addition to myopia, children born prematurely also tend to develop another refractive errors, such as hyperopia, astigmatism, and anisometropia.[65] The incidence rate of anisometropia is higher in patients with ROP and increases with the severity of ROP. Moreover, it has been documented that the prevalence of strabismus increases in low BW population. Patients with laser treatment have a higher incidence of myopia, ETROP study found that at 3 years of age the prevalence of myopia in infants with severe ROP was 65%–71% and the prevalence of high myopia (< -5.00) was 51%.[66] Intravitreal anti-VEGF agents, specifically bevacizumab was evaluated for refractive error development in a meta-analysis, compared with laser-treated children, IV bevacizumab-treated children have less myopic refractive error, lower prevalence of high myopia, and less astigmatism.[67]

Cerebral visual impairment is recognized in preterm individuals, hypoxia selectively injures the periventricular deep white matter causing brain lesions known as periventricular leukomalacia, the reported incidence ranger from 4% to 15%.[68] Contributing factors to retinal detachment include atrophic holes within peripheral avascular retina, visible vitreous condensation ridge-like interface with residual traction and premature vitreous syneresis. Prospective studies are needed to explore benefit of prophylactic treatment.[69]

Children with regressed ROP are more vulnerable to vitreoretinal complications such as retinal ears, retinal detachment, and vitreous hemorrhage in the long term. Retinal tears may be due to the failure of the scarred retina to expand along with the postnatal expansion of the eyeball. The localization of the tears is equator and posterior types.

Deficits in visual acuity in low-birth-weight children persists even in the absence of ROP or known neurological abnormalities.[70] Visual field defects, usually affecting the lower field, have been reported in premature children with visual impairment due to white matter damage of immaturity also known as periventricular leukomalacia.[68] The reduction associated to treatment was evaluated in the cryotherapy, data from eyes with quantifiable visual fields indicate that cryotherapy produces a small reduction of visual field area in eyes with severe ROP.[71] Later, the ETROP compare visual field extent at 6 years of age in eyes with high-riks prethreshold ROP randomized to early treatment with eyes that underwent conventional management and regressed without treatment and they found the early treatment for high-risk prethereshold ROP does not adversely affect visual field extent clinically.[48] Hence, it remains a matter to discuss if the visual field decrease is due to the retinal damage associated with prematurity and not the associated treatment in patients.

FUTURE

One of the main obstacles is how to provide the appropriate neonatal care these patients must have; many of them with a tortuous course of different pathologies, which makes them find themselves in hospital units with many needs, among which the deficiency of certain basic medical equipment (such as oxygen blenders) worsens our patient's ophthalmological diagnosis. Another of the main problems is the lack of trained



Figure 6: Retinal laser photocoagulation training with indirect ophthalmoscope with live anesthetized rabbits under the care of veterinarians

ophthalmologists to carry out adequate screening, accurate diagnosis, and treatment. International ophthalmology trainees perform a limited number of ROP examinations and laser interventions, limited ROP training among ophthalmologists may lead to misdiagnosis and ultimately mismanagement of a patient. Loss of vision and exposure to unwarranted treatments are among the implications of such errors. We need to improve ROP screening and treatment training, in the ophthalmology residency programs.[72] Efforts currently being carried out are to train more personnel in the neonatal intensive care unit, to rely on telemedicine for screening and referral of these patients. Animal models for surgical training in transpupillary laser photocoagulation with indirect ophthalmoscope, could be a safe way to train ophthalmologists in retinal photocoagulation [Figure 6]. There are still many limitations for the diagnosis and treatment of these patients, but the progress that exists in knowing the main obstacles, the results of the implemented treatments has led to a constant evolution of the diagnosis and treatment of the pathology since its description.

CONCLUSIONS

ROP is one of the leading yet preventable causes of childhood blindness worldwide, especially in developing countries. Despite significant improvements of medical care, preterm infants are at a greater risk to develop health chronic conditions that could lead to permanent disability. NICU team lead by neonatologists and specialized nurses, need to continue working with trained ophthalmologists to provide the best health care in this fragile preterm population, and governmental public policies should assume responsibility to guarantee high quality care for all newborns.

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Conflicts of interest

There are no conflicts of interest.

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Acute traumatic maculopathy

ABSTRACT

Traumatic retinopathy may occur secondary to direct or indirect trauma to the globe. Presentation of retinopathy may either be a coup (direct site of injury) and or contre-coup (distant sites including the macula). Commotio retinae in the posterior pole is referred to as Berlin's edema. The fovea is extremely thin, and blunt trauma may cause a full-thickness macular hole by either one or a combination of mechanisms, including contusion necrosis and vitreous traction. Holes may be noted immediately or soon after blunt trauma due to severe Berlin's edema, or after a subretinal hemorrhage caused by a choroidal rupture, or following severe cystoid macular edema, or after a whiplash separation of the vitreous from the retina. Post-traumatic macular holes (TMHs) may be successfully closed with vitrectomy and gas injection. We report a case of blunt trauma leading to Berlin's edema and TMH.

Keywords: Berlin's edema, blunt trauma, traumatic macular hole

A 20-year-old male patient presented with an injury to the left eye with a cricket ball following which he experienced a sudden loss of vision. He had a visual acuity of 20/400 in the left eye. On evaluation, anterior segment was normal. Fundus evaluation revealed Berlin's edema with traumatic macular hole (TMH) [Figure 1a]. Optical coherence tomography (OCT) macula revealed full-thickness macular hole with retinal thickening and para-foveal disruption of the outer segment [Figure 1b].

Blunt trauma causes expansion of the globe in the equatorial region, which leads to a combination of anteroposterior vitreoretinal and tangential retinal traction, leading to a central defect in the fovea.[1,2]

CLINICAL FINDING

This acute traumatic maculopathy presented with TMH with Berlin's edema.

Clinical

Fundus examination reveals glistening gray-white opacification of the neurosensory retina in the macula region, mimicking a pseudo cherry-red spot with a round or ellipsoid full-thickness defect of the neurosensory retina [Figure 1a].[3]

Optical coherence tomography

Optical coherence tomography (OCT) macula revealed full-thickness macular hole with retinal thickening and parafoveal disruption of the outer segment [Figure 1b].

Sequelae

At 3 months follow up, patient presented with a fundus photograph [Figure 2a] revealing macular scarring with reduction of glistening cherry red spot and resolved disc haemorrhages. The OCT macula [Figure 2b] revealed macular

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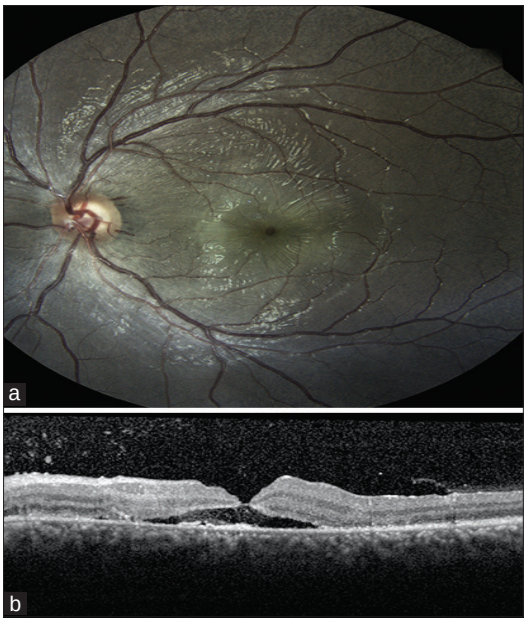


Figure 1: (a) Color fundus photograph OS showing yellowish discoloraton of macula with central red lesion revealing Berlin's edema and traumatic macular hole with disc haemorrhage. (b) Optical coherence tomography (OCT) macula revealed full-thickness macular hole with retinal thickening and para-foveal disruption of the outer segment

scarring with complete disruption of the outer segment and inner segment /outer segment junction.

Seen in

This condition is seen in activities associated with blunt trauma to the face and orbits, especially high-impact sports activities (commonly ball sports), violence, and motor vehicle accident.

Who described it?

- Berlin's edema - First described by Berlin in 1873
- Macular hole - First described by Knaap in the late 1869 and later described by Noyes in 1875.

Cardinal diagnostic features?

Diagnosis is clinical and is made based on the characteristic appearance. However, OCT is imperative in diagnosing and managing this disorder. It provides a high-resolution image for the evaluation of macula in cross-section and three-dimensional view. OCT can help detect subtle TMHs as well as stage obvious ones.

Why it occurs?

Blunt trauma causes displacement of the lens-iris diaphragm with the expansion of peripheral structures outward. This causes stretching and tearing of ocular tissues, secondary to vitreoretinal deformation caused by the transmission of hydraulic forces. The retina is inelastic and absorbs the full effect of shock waves, resulting in injury to

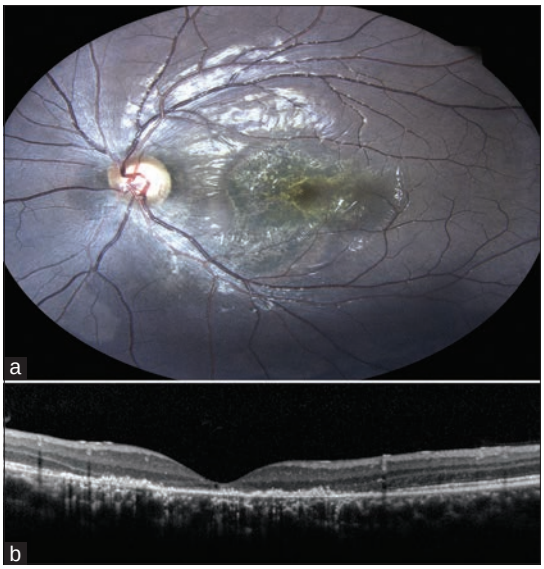


Figure 2: (a) Color fundus photograph OS showing yellowish discoloraton of macula with central red lesion revealing Berlin's edema and traumatic macular hole with disc haemorrhage. (b) Optical coherence tomography (OCT) macula revealed full-thickness macular hole with retinal thickening and para-foveal disruption of the outer segment

various layers mainly the outer segment of photoreceptor andretinal pigment epithelium (RPE) junction causing Berlin's edema.

The hypotheses behind the development of TMHs are the tangential and anteroposterior vitreoretinal traction.

What else to examine?

Rule out the seven rings of trauma:

1. Sphincter pupillae tear
2. The iris base for iridodialysis
3. Anterior ciliary body trauma
4. Separation of ciliary body from scleral spur
5. Trabecular meshwork tear/flap
6. Zonular dialysis
7. Retinal attachment at ora serrata.

Declaration of patient consent

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

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Conflicts of interest

There are no conflicts of interest.

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Major Review

Designing clinical trials

ABSTRACT

A clinical trial is the gold standard study design to assess the effectiveness of interventions in health care. Yet, often paradoxically, clinicians find that the benefits of the randomized controlled clinical trial cannot be replicated in an actual clinical practice. A tradeoff between practicality and ideal trial requirements is needed to develop a pragmatic clinical trial. The results of a pragmatically constituted trial are more likely to be acceptable to practicing clinicians. The major steps and requirements and practices for a clinical trial by clinicians are summarized in this article. The PICOT format is a helpful approach to summarize research questions that explore the effects of therapy. Next, depending on the feasibility, the study population is selected by using inclusion and exclusion criteria. The needed sample size is calculated from this representative study population by providing clinical data inputs to a statistician. It is essential that chance, all possible forms of bias and confounding factors are eliminated or balanced between the study groups. This is ensured by randomization, proper allocation concealment, and masking. A clinical trial also needs to pass through relevant review boards and should be ethical. The good clinical practice guidelines throw light on this aspect. Finally, it is very important that a clinical trial is reported adequately such that readers understand the trial's design, conduct, analysis and interpretation, and can assess the validity of its results. The CONSORT guidelines are very useful in this regard.

Keywords: Bias, clinical trials, randomisation

INTRODUCTION

A clinical trial is the gold standard study design to assess the effectiveness of interventions in health care.[1,2] It is a planned experiment that determines the magnitude and direction of difference between the application of an intervention and a comparator group. The comparator group is often the current standard of interventions or an acceptable standard of intervention or a placebo.[3] The clinical trial design thus includes the new intervention and the control intervention, and the group that receives the new intervention and the comparator group.[4] In this manuscript, we will look at the essential elements of the design of a clinical trial with specific focus on its applicability in a clinical practice setting.

WHEN SHOULD WE DO A CLINICAL TRIAL?

A clinical trial must be considered when we want to assess the efficacy of a new intervention in comparison to an already existing intervention. Some modalities of therapeutic or diagnostic intervention are available for most medical conditions. It is rare that a medical condition may not have any existing diagnostic or therapeutic process involved in its management although the standards of care may differ between health-care settings and countries. The comparison of a new intervention must be against the locally relevant standard for that medical condition.[5,6] The use of a placebo or comparing interventions against no interventions are not considered ethical and are to be done only if necessary.[7]

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PHASES OF A CLINICAL TRIAL

There are several phases in a clinical trial. It is important to understand the different phases of a clinical trial although clinicians are mostly concerned with phase 3 trials.[6,8,9]

Pre-phase 1 trials

These trials are done on animals and are basically used to study the effect of the drug molecule on each level of the organization in the body, i.e., from the cell to the organ systems, and the effect of the body on the drug molecule. In this phase, the lethal dose of the drug needed to kill 50% of the animals is determined. This is called LD50 and the drug undergoes further testing if the LD50 is much higher than the dose required for the desired purpose in the body and if the pharmacokinetic and pharmacodynamic effects are favorable.

Phase 1 trials

This is done on healthy volunteers or on persons with serious forms of disease who are not improving with any available treatment. The same pharmacokinetic and pharmacodynamic effects are evaluated as was done in pre-phase 1. The drug is given in increasing doses till the results obtained in animals are now obtained in humans.

Phase 2 trials

The drug is now given to a greater number of people usually in the hundreds. The molecule is given to those people in whom it was intended rather than healthy volunteers. The proportion of patients who achieve the desired results at the set dose and those who do not achieve it are determined. Any adverse reactions in this group are noted.

Phase 3 trials

This is a planned experiment on humans with sufficient sample size and power to prove or disprove the predicted benefits of the molecule. The results of these trials are submitted to regulatory authorities for approval of the interventions.

Phase 4 trials

Phase 4 trials are the post marketing surveillance that looks to identify rare or serious adverse effects, drug-drug or diet-drug interactions. Very importantly, a wider spectrum of population is studied in this phase. Hence, a drug or an intervention can be declared as safe only if it has passed through enough years of postmarketing surveillance.[10]

THE DESIGNS OF A TRIAL

There are few possibilities when we assess the effectiveness of an intervention. The new intervention may be superior to an existing intervention. The new intervention may perform exactly like an existing intervention or may be equivalent to an existing intervention. The new intervention may be nearly similar to an existing intervention, within a margin of acceptability, or is noninferior to an existing intervention. The new intervention may be inferior to the existing intervention. It is important to define the margins of superiority and noninferiority to determine if a new intervention is superior or noninferior. These margins are determined based on clinically relevant outcomes, the quantum of change that is considered as clinically acceptable and may change based on the clinical condition of interest. They may also be influenced by the prevalence of the condition, the severity of the condition and the cost of the intervention. If the condition is mild with milder sequelae and a milder natural progression, we could aim for a larger margin of superiority.[11] If the condition is more severe, with high fatality or severe adverse events, or a rapid natural progression, we may aim for a smaller margin of superiority or a larger margin of noninferiority so that any small improvement may impact favorably on the patient. We must also consider the cost of the newer intervention while determining the margins of superiority and noninferiority. We may consider a larger margin of superiority if the new intervention is much costlier than the existing intervention.

Common clinical trial designs are therefore either superiority designs, noninferiority designs, or equivalence trials. The superiority trial aims to establish that the new intervention is significantly better than an existing intervention based on a predefined margin of clinical relevance. As an example, let us consider that the current standard of care provides good outcomes in 35% of those who receive the intervention. We may predefine superiority as more than 45% good outcomes in those who receive the new intervention. In this instance, we will consider the new intervention as useful only if it leads to good outcomes in more than 45% of those who receive the intervention. The noninferiority trial aims to establish that the new intervention is not inferior to the existing intervention.[12] As an example, we can predefine non inferior as a margin of $\pm 10\%$ and conclude that the new intervention is comparable to the existing intervention if outcomes are $\pm 10\%$ of that with the existing intervention. The outcomes with the new intervention maybe slightly superior, equivalent, or slightly inferior compared to the existing intervention. In a superiority design saying that there is no difference does not conclude that the interventions are noninferior.[13] Similarly, in a noninferiority design even if we find that one intervention is statistically significantly better than the other, we cannot conclude that the newer drug is superior to the existent drug.[14] We must conduct a larger study with an appropriate sample size to confirm this.

IDEAL VERSUS PRAGMATIC TRIAL

Clinicians often find that results obtained and reported from a strictly controlled environment of a clinical trial does not translate to equal results in an actual clinical practice setting. The clinical trial is a well-regulated controlled environment while clinical practice settings are not often a strictly controlled environment. Interventions in a clinical trial are tested on subjects with strict inclusion and exclusion criteria, and strict regulation of follow-up. In a real-life clinical setting, patients may not always fall into the strict boxes of inclusion and exclusion set out in a trial. In a pragmatic setup, a clinician wants to know how the intervention will perform in a clinical setup that caters to a wide-ranging variety of population.

DESCRIPTION OF INTERVENTIONS

It is important to have noticeably clear, precise descriptions of the interventions and comparators. This will help ensure that there is no overlap between the groups that can possibly lead to a misclassification bias and that outcomes truly represent differences between the groups.

The PICOT format is a helpful approach to summarize research questions that explore the effect of therapy:

- (P)– Population refers to the sample of patients we wish to recruit for the study
- (I)– Intervention refers to the treatment that will be provided to subjects enrolled in the study
- (C)– Comparison is the treatment that we are comparing with the intervention (I). This is also called the control group. If an existing treatment is considered the "gold standard," then, it should be the comparison group
- (O)– Outcome represents what variables we plan to measure to understand the effectiveness of the intervention
- (T)– Time describes the duration for the data collection.[15]

OPERATIONAL DEFINITIONS

We must describe in detail the interventions and comparators, their assessments and ascertainment, define the outcomes of interest and their assessments and ascertainment. Use standard definitions or standard methodologies if they are available. The possible adverse outcomes and methods of assessment and ascertainment must be defined.

SELECTION OF STUDY POPULATION

The selection of the study population is an important aspect of the clinical trial. The study population must be of adequate size such that random error is eliminated and that any identified differences are true differences between the groups. This is ensured by sample size calculation about which I shall discuss shortly. The study population must be representative so that the study results can be extrapolated to the general population.[16]

SO HOW DO WE SELECT A STUDY POPULATION?

We must define certain clinical and demographic criteria based on our research question. We also devise certain geographic (e.g., selection of patients coming to the glaucoma clinic of a tertiary care center only) and time bound strategies (e.g., selection of patients coming between January 2021 and December 2021). These four strategies determine our inclusion criteria. To this subset of population, we apply certain exclusion criteria. Usually, we exclude patients whom we think might affect the quality of our data or acceptability of our study or the success of follow-up. This group that we finally obtain is the study population. Ideally, we exclude subjects (based on a clinical determination by the managing physician) who definitely will benefit from the new intervention or subjects who definitely will not benefit from the new intervention. Subjects who state a preference for either the new intervention or the existing intervention are also excluded from a clinical trial to reduce any bias.

The study population may be drawn from a contained geographic zone or from multiple geographic zones. The study population may be drawn from a single center or from multiple centers. We must be pragmatic in deciding which scientific and which practical decisions regarding inclusion and exclusion criteria are to be selected to obtain a representative sample. Considering only purely scientific criteria can provide good internal validity but cannot be generalized to the population, i.e. there is minimal external validity. On the other hand, considering purely practical criteria may have poor internal validity and reproducibility of results. Obviously, this balance depends not only on the methodology but also on the research question and design of the study.[17]

Further, to maintain a representative sample, we also must periodically monitor the recruitment strategy and address "lost to follow-up." These strategies must be incorporated right from the design of study to its implementation. They may include incentives to patients and repeated sustained contact interactions with patients.[18]

SAMPLE SIZE CALCULATION

Sample size estimation is an important part of clinical research. This requires some logical thinking and some information

which the investigator should know before starting the study. The sample size estimates include the identification of the variable or outcome you want to study including the primary and secondary outcomes. The expected frequency of the study variable and the proposed differences between study groups (effect size) of clinical relevance are predefined before the trial. Then give a desired precision of the estimate, for example, the Standard Deviation. These are usually obtained from a review of the literature. If this is unknown, a pilot study may have to be done to derive estimates from your own population. Rarely, if it is thought that if the population is normally distributed then we consider that the range is six standard deviations. The lesser the precision of the estimate needed the smaller the sample size would be. Then indicate the degree of certainty you want about the desired precision. Adjustments must be made for population size, design effect and expected response rate. To summarize, the sample size estimation requires the primary outcome measure, alpha and beta errors, the power of the study, and the proposed differences between study groups. The anticipated margins-superiority margins, inferiority margins, and allocation ratio are other considerations to determine the sample size. There are several software (commercial and free) programs that help with the sample size estimation for clinical trials. However, it is recommended to consult a biostatistician at the design stage of a clinical trial to make sure that the appropriate sample size is estimated after considering all necessary inputs. We must remember that the sample size estimation is a statistical calculation that is based on clinical data inputs.[19]

RANDOMISATION, ALLOCATION CONCEALMENT AND MASKING

Randomization of the patients into discrete study groups is the cornerstone of an randomized controlled trial (RCT).[20] This is the process where the patient has an equal chance of being assigned to any one of the study groups. This means that the groups are similar with reference to known and unknown prognostic factors. The first step is the generation of a random sequence. Simple strategies of allocation can include tossing a coin or odd and even number approach but are not recommended as a practice. A truly random number sequence can be obtained from computer generated programs that include a random number table or from sites like www. RANDOM.org. The randomization generation can start from a changing seed or a static seed, can be based on unequal or equal intervals or blocks and can be with replacement or without replacement. Besides randomization, we can choose to allocate subjects equally between the intervention arms, for example, in a 1:1:1 ratio. We can also opt for allocation ratios of 1:2 or 1;3 based on the prevalence of the condition.

The randomization sequence must be such that the investigator is unaware of the sequence of allocation of participants into any of the arms of the study before and until the assignment is complete. A plan of allocation concealment must be stated in the protocol. The modern modes of allocation concealment include centralized or remote telephone based or computer based or web-based allocation systems. Sequentially numbered opaque sealed envelopes, though easy and cost effective have a greater risk of failure. Since we have a pair of eyes, we can choose to study the effects of intervention in one randomly selected eye and use the other eye as control. The goal of allocation concealment is to prevent selection bias. Furthermore, without allocation concealment, there is every chance that the effects of the intervention are overestimated or underestimated.[21]

Masking (previously called blinding) is aimed at preventing ascertainment bias. This means that investigators, patients, or anyone who can directly or indirectly influence the conduct and outcome of the study are prevented from knowing about the patient's allocation.[22] There is no standard definition of the terms such as single blind or double or triple blind. We must explicitly define who was masked. Double blind does not necessarily mean that the patient and investigator are masked. It could be the patient and the outcome assessor who might have no direct contact with the patient. An open-label trial means that the investigator and the patient know to which intervention the patient is assigned. It is important to remember that masking cannot always be incorporated into a RCT. This is especially so when the intervention is a surgery.[23]

RANDOM ERROR, BIAS AND CONFOUNDING

Before we talk of bias and chance, we must know the meaning of validity, both internal and external. Having internal validity means that methods have been employed to minimize errors made by the patients or investigators or those who have conceptualized or analyzed the clinical trial. In other words, maximum work has been made to make the study accurate. External validity means the extent to which the results of our clinical trial can be used to generalize to the population.[23] Bias is the error introduced into the study by the patient and/or the investigator such that the association between the independent and dependent variables is incorrectly estimated.[24] This can also be a systematic error. Type 1 error or alpha error causes the null hypothesis to be rejected even though no true difference exists between groups. Here, the conclusion is false positive. Type 2 error or beta error causes the null hypothesis to be accepted even though a true difference exists between groups. This is a

false-negative conclusion. Null hypothesis is the opposite of what we expect from the study.

The two most important types of bias are the selection bias and information bias. Selection bias leads to a difference in the baseline characteristics between the study groups. These are the demographic and clinical characteristics. Information bias can be dealt by providing precise operational definitions of variables, or detailed measurement protocols. It also needs repeated training of the personnel involved in the trial and data audits and cleaning.

A variable that directly influences the relationship between an independent variable and the primary outcome variable is a confounder. Confounding is the confusion of effects.[25] It can cause overestimation or underestimation of effects or in a bad case scenario, completely change the direction of an effect. Randomization which aims to make the intervention and control groups as similar as possible ensures that confounding factors are also similarly and evenly distributed between the groups. If we think that a given factor is likely to be a confounder then we can select groups that contain/do not contain the given factor. This process is known as restriction. The only way to account for the influence of confounders in the analysis stage is by performing analysis that adjusts for the effects of the confounders and their interactions. Finally, it must be remembered that unless we take the entire population into consideration, the chance of an unknown variable affecting the outcome cannot be eliminated.[26]

COMPLIANCE

Compliance is ensured by maintaining treatment logs after enrollment.

MANUAL

A precise standard operating Procedure must always accompany a protocol which will provide a detailed description of the path taken by the patient when they present at the clinic. A CONSORT flow diagram showing in detail the steps of enrollment, intervention and analysis is an extremely helpful adjunct to the manual.

ETHICS IN CONDUCTING A CLINICAL TRIAL

The good clinical practice (GCP) guidelines published by the International Council of Harmonization (ICH) is a document that helps regulate clinical trials. The GCP is a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of the trial subjects are protected.[27]

Today, the ICH-GCP guidelines are used in clinical trials throughout the world with the main aim of protecting and preserving human rights.

REVIEW BOARDS

The clinical trial passes through a scientific review by the Institutional Research Committee. It determines if the research question, study design, and methodology are good or not. Next, it undergoes an ethical review by the Institutional Ethics Committee. This is to ensure the safety and welfare of research participants. The trial must be registered in Clinical Trials Registry-India http://www.ctri.in/before enrollment of the first subject. Registration in the following trial registers is also acceptable: http://www.actr.org.au/; http://www.clinicaltrials.gov/; http://isrctn.org/; http://www.trialregister.nl/trialreg/index.asp; and http://www.umin.ac.jp/ctr.

Depending on the nature of intervention, the trial may have to pass through regulatory reviews conducted by the Drug Controller General of India, or Screening Committees instituted by the Ministry of Health, Government of India.

CONSORT CHECKLIST

This is a list of items that editors of journals expect to be strictly reported by the authors of an RCT. The CONSORT (CONsolidated Standards of Reporting Trials) 2010 guideline is intended to improve the reporting of parallel-group RCTs, enabling readers to understand a trial's design, conduct, analysis and interpretation, and to assess the validity of its results.[28] It contains a 25-item checklist and flow diagram, freely available for viewing and downloading. There is an accompanying explanatory and elaboration document - intended to enhance the use, understanding, and dissemination of the CONSORT statement - which presents the meaning and rationale for each new and updated checklist item providing examples of good reporting and where possible, references to relevant empirical studies. Several examples of flow diagrams are also included.[29]

CONCLUSION

Randomization is considered the most powerful design in clinical trials. If all the variables have been carefully distributed equally between the groups by utilizing this process, then the differences in the outcome can only be due to the intervention.

In the hierarchy of evidence for clinical interventions, they constitute the best process for seeking the truth.[30] All the stakeholders in a clinical trial need to ensure that trial outcomes are developed with patients in mind, that unbiased methods are adhered to, and that results are reported in full and in line with those prespecified at the trial outset.[31]

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Conflicts of interest

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Major Review

Retinal manifestations of COVID-19 disease - A review of available information

ABSTRACT

Ocular signs and symptoms have been reported in COVID-19 patients, and there is a surge of information about corneal, uveal, retinal, and neuro-ophthalmological involvement in COVID-19 infection. This review attempts to determine from various researches published during the time of the pandemic, the retinal manifestations of COVID-19 infection, and its significance and correlation to severity of systemic disease. An extensive search strategy was employed using keywords "novel corona virus", "COVID-19", "SARS CoV2," or "retina," either singly or variably combined, to retrieve the articles of retinal manifestations of COVID-19 published from January 2020 till date. Retinal manifestations are ubiquitous and include microangiopathy, occlusive vascular conditions, alterations in vascular caliber, and capillary density, among others. They seem to correlate with disease severity and reflect on similar changes in other parts of the body as well. Newer studies are bringing out more and more evidence of hitherto unknown retinal manifestations of COVID-19 disease.

Keywords: COVID-19, novel coronavirus, retina, SARS CoV2

INTRODUCTION

One of the most significant medical events in the present times is the emergence of the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS CoV2) causing coronavirus disease 2019 (COVID-19).[1] The first cases, presenting as pneumonia of unknown origin, were identified in Wuhan, the capital city of Hubei province in China.[2] This condition is now recognized as a pandemic, and there are almost 113,467,303 confirmed cases of COVID-19, including 2,520,550 deaths, reported to the WHO.[3] The clinical features of COVID-19 are manifold, ranging from being completely asymptomatic to acute respiratory distress and multiorgan dysfunction. The presenting symptoms range from fever, cough, dyspnea to headaches, fatigue, myalgia, and even conjunctivitis.[4] Ocular signs and symptoms have been reported in COVID-19 patients, and there is increasing recognition of conjunctivitis as a prodromal symptom of this disease.[5] As this is an ongoing pandemic, there is a lot of information accumulating on a regular basis, with newer researches contributing to better understanding of the disease process. Animal studies have shown that coronaviruses can cause a variety of ocular manifestations such as conjunctivitis, anterior uveitis, retinitis, and optic neuritis.[6] The same could be extrapolated to human infections, and recent researches are in fact providing increasing evidence of the same. The SARS CoV2 virus has a high affinity for the ACE2 receptors, and these receptors are seen in retinal vascular endothelial cells and choroid, besides other locations.[7,8] In a study of retinal biopsies conducted on 14 eyes of patients who died from COVID-19 infection, viral RNA was discovered in three eyes, thus proving beyond doubt that the SARS CoV2 virus can affect the retina.[9] Recent studies show that COVID-19 virus can affect structures such as the cornea, uvea, retina, and the optic nerve, besides the conjunctiva. This review attempts to

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determine from various researches published during the time of the pandemic, the retinal manifestations of COVID-19 infection, and its significance and correlation to severity of systemic disease, if any. An extensive search was employed to retrieve articles of COVID-19 published from January 2020 to date using the keywords "novel corona virus," "COVID-19," "SARS CoV2," or "retina," either singly or variably combined.

METHODS

The aim of this study was to review the available data on the retinal signs and symptoms in COVID-19 infection, demographics, its significance, and correlation to severity of systemic disease, if any.

Search strategy

An extensive search was employed to retrieve articles of COVID-19 published from January 2020 to date. The search strategy included the following keywords "novel corona virus," "COVID-19," "SARS CoV2," or "retina," either singly or variably combined. Databases searched included PubMed, Scopus, Embase, and the Saudi Digital Library.

Inclusion criteria and exclusion criteria

Cross-sectional studies, case series, or case reports of patients with COVID-19 infection having retinal signs on ophthalmoscopy, fundus photography, FFA, OCT, or OCT angiography (OCTA) were included in this review. However, studies of other designs or those not demonstrating retinal signs of COVID-19 infection or studies demonstrating the effect of medications used in COVID-19 treatment on the retina were not included. Similarly, researches not in the English language or in which an English translation could not be obtained were excluded as well.

RESULTS

After applying the inclusion and exclusion criteria, 19 researches were included in this review. They included 5 cross-sectional studies, 2 case series, and the remaining case reports.

The researches involved 260 COVID-19 patients in all. Of the five cross-sectional studies, two were from Italy and one each from Brazil, Spain, and Iran [Table 1].[10-14] Both the case series were from Brazil [Table 2].[15,16] There were 12 case reports included in this review, which were from various parts of the world, such as Spain, Brazil, France, Italy, and India [Table 3].[17] Three of the cross-sectional studies focused on the retinal vascular signs of COVID-19, which included reduction in the radial peripapillary capillary plexus (RPCP) density, decrease in foveal and parafoveal superficial and deep capillary plexus (SCP and DCP) density, and increase in retinal arterial and venous caliber.[11-13] In a case series reported from Sao Paulo by Marinho *et al*., retinal and OCT changes were noted in 12 patients (age group 25–69 years), 11–33 days after developing symptoms of COVID-19.[16] The case reports showed the presence of retinal manifestations such as cotton wool spots and retinal hemorrhages in COVID-19 patients.[17,18] Vascular changes such as impending CRVO, papillophlebitis, and even bilateral CRVO were reported in five case reports.[20-25] Other retinal manifestations reported include chorioretinitis, outer retinal abnormalities, and panuveitis.[26-28]

DISCUSSION

Over the past couple of months, there is increasing evidence of posterior segment involvement in COVID-19 infection. The incidence of retinal involvement ranged from 7% to almost 55% in different studies.[10,12,14] However, a higher incidence of retinal involvement was noted in studies on more serious/critical patients.[10] Lani-Louzada *et al*. noted an incidence of 22% retinal involvement in a case series of 47 eyes of severe or critical COVID-19 cases.[15] This points to a correlation between the severity of COVID-19 disease and the incidence of retinal involvement. Some authors consider conjunctivitis to be an association of more severe SARS CoV2 infection and an indicator of the severity of the disease.[29-33] Similarly, it is probable that retinal involvement parallels involvement of other organ systems and points to a more severe disease course. Retinal findings associated with COVID-19 infection include retinal hemorrhages and cotton wool spots, which is indicative of a microangiopathy-like picture.[10,12,14] The retinal changes are thought to be due to the effect of the virus itself or the profound inflammatory response that occurs as part of the disease process. However, some researchers speculate that the retinal changes are unlikely to be due to the direct effect of the virus, due to the associated inflammation and accompanying cytokine storm along with the hypercoagulable state, all of which contribute to the pathogenesis of organ damage.[10,15] It is now proven conclusively that retinal involvement is a part of COVID 19 disease; thus, retinal examination, either by ophthalmoscopy or retinal imaging, should be a part of the workup of COVID-19 patients complaining of new-onset blurred vision, dyschromatopsia, defective near-vision, or scotomata.

Retinal vascular changes accompanying SARS CoV2 infection were studied in three cross-sectional studies. Using OCT and OCTA, Savastano *et al*. in a cross-sectional study of 80 Italian subjects 1 month after recovery from COVID-19 noted that there was a reduction in retinal peripapillary capillary

Table 1: Cross-sectional studies of coronavirus disease 2019 patients with retinal manifestation

Name of study	Type of study	Number of participants	Results	Inference
Pereira *et al*.[10]	Cross-sectional study (Brazil)	18 patients with severe COVID-19 disease	55.6% of the patients had retinal abnormalities such as flame-shaped hemorrhages, cotton wool spots, and sectoral retinal pallor	The retina was affected in a significant number of patient, but the authors suggest that the retinal changers could be due to the severe inflammatory response and not due to direct viral replication per se
Savastano *et al*.[11]	Cross-sectional study (Italy)	80 patients (1 month after recovery from COVID-19 infection)	RPCP perfusion density was lower in SARS CoV2 patients compared to controls). Average RNFL thickness correlated with the RPCP density	The findings probably point to damage at the retinal microvascular level due to the COVID-19 infection and more studies are needed to confirm this hypothesis
Invernizzi *et al*.[12]	Cross-sectional study (Italy)	54 COVID-19 patients and 133 unexposed subjects	Retinal arterial and venous diameter was more in COVID-19 patients compared to controls. Retinal hemorrhages and cotton wool spots were noted in about 7%–9% of cases	There seems to be a direct correlation between retinal venous diameter and the disease severity. This could be related to the virus or to the inflammatory process
Abrishami *et al*.[13]	Cross-sectional study (Iran)	31 patients who recovered from COVID-19 infection	Mean SCP and DCP density in foveal and parafoveal regions using OCTA was significantly lower in COVID-19 patients compared to cohorts	The authors hypothesize that the vascular changes could be due to the effect of the virus itself or the effect of inflammatory response
Landecho *et al*.[14]	Cross-sectional study (Spain)	27 COVID-19 patients with respiratory symptoms after 14 days of discharge from the hospital were examined with fundoscopy, OCT, and OCTA	5 patients (22%) developed cotton wool spots. No other retinal signs were noted. The cotton wool spots could point to the presence of a microangiopathy picture in these patients	The authors suggest that the microangiopathy could be a direct effect of the virus affecting the endothelium or it could represent the effect of a hypercoagulable state which occurs as part of the disease process

COVID-19 – Coronavirus disease 2019, RPCP – Radial peripapillary capillary plexus, RNFL – Retinal nerve fiber layer, SCP – Superficial capillary plexus, DCP – Deep capillary plexus, OCT – Optical coherence tomography, OCTA – OCT angiography

Table 2: Case series of coronavirus disease 2019 patients with retinal manifestations

No	Name of study	Type of study	Number of participants	Results	Inference
1	Lani-Louzada *et al*.[15]	Case series (Brazil)	47 eyes of 25 severe or critical hospitalized COVID-19 patients	Retinal changes were noted in 12% of patients - nerve fiber layer infarcts, flame-shaped hemorrhages, and microhemorrhages	Retinal vascular changes were noted in a significant proportion of severe or critical COVID cases and they were probably due to the therapeutic interventions or comorbidities
2	Marinho *et al*.[16]	Case series (Brazil)	12	Retinal and OCT changes were noted in 12 patients 11–33 days after developing symptoms of COVID-19	The OCT changes could be associated with the neurological manifestations of COVID-19

OCT – Optical coherence tomography, COVID-19 – Coronavirus disease 2019

plexus (RPCP) density in SARS CoV2 patients compared to controls. Among the COVID patients, lower RPCP density was noted among patients treated with lopinavir and ritonavir, antiplatelet medications, and also in older patients and those with hypertension.[11] All these factors point to microvascular damage in COVID disease, which is aggravated by therapy and preexisting risk factors. In yet another cross-sectional study employing fundus photographs of 54 admitted and swab-positive COVID-19 patients from Italy, retinal arterial and venous diameter was noted to be more in COVID-19 patients as compared to controls.[12] Venous caliber was larger in more serious cases, and the timing of the maximal venous diameter correlated with the peak inflammatory response in the disease process. In a research from Iran conducted using OCTA on 31 COVID-19–recovered patients, the mean SCP and DCP densities in foveal and parafoveal regions were significantly lower in COVID-19 patients compared to cohorts. The OCTA was conducted at least 2 weeks after recovery from COVID-19. The vascular changes were hypothesized to be due to the virus itself or the inflammatory response to the virus. These studies also highlight the susceptibility of the retinal vasculature to the virus and highlight the virus affinity for the ACE2 receptors in the vascular endothelium. Similar vascular changes could probably be existing in blood vessels of other organ systems and ACE2 receptor rich sites, as well, and retinal examination could provide an insight into the effect of virus on the vascular system, in general.

In a case series from Sao Paulo by Marinho *et al*. published in May 2020, retinal and OCT changes were described in 12 patients seen 11–33 days after the start of COVID-19 symptoms.[16] Four patients showed cotton wool spots and

Table 3: Case reports of coronavirus disease 2019 patients with retinal manifestations

No	Name of study	Type of study	Characteristics of the patient	Results	Inference
1	Gascon *et al*.[17]	Case report (France)	53-year-old man	Ophthalmoscopy showed retinal hemorrhages, and OCT revealed AMN and PAMM like lesions. Roth spots were also seen	The authors suggest that COVID-19 infection could play a role in retinal vascular damage and lead to the complications such as AMN, PAMM, and Roth's spots
2	Gonzalez-Lopez *et al*.[18]	Case report (Spain)	50-year-old man	Fundus examination revealed peripapillary cotton wool spots in both eyes with RNFL on OCT and decreased SRCP flow in OCTA	The authors suggest that retinal microvascular changes could help understand the pathogenesis of COVID-19 organ damage
3	Virgo and Mohamed[19]	Case report (UK)	Case 1: 37-year-old Caucasian female, Case 2: 32-year-old Caucasian male	Case 1: OCT showed a picture of PAMM Patient 2: OCT showed a diagnosis of AMN	These 2 cases probably reveal the postinfectious complications of COVID-19 disease
4	Insausti-García *et al*.[20]	Case report (Spain)	40-year-old man	The patient presented with decreased vision sensitivity in one eye. A diagnosis of papillophlebitis was made. Both macular and disc edema responded to intravitreal dexamethasone injection	The authors suggest that the triad of endothelial damage, cytokine storm, and hypoxia play a role in the coagulopathy of COVID-19 disease
5	Invernizzi *et al*.[21]	Case report (Italy)	54-year-old woman	There was a unilateral scotoma and defective vision. Fundoscopy and imaging showed retinal hemorrhages and whitening and a fernlike pattern on autofluorescence, which is typical of impending CRVO	This could represent a thromboembolic complication of the disease process. The authors stress the role of Virchow's triad in pathogenesis and emphasize the importance of looking for retinal thromboembolic phenomena
6	Sheth *et al*.[22]	Case report (India)	52-year-old male	Ophthalmoscopy showed inferior hemi-RVO, superonasal BRVO, and macular edema. SD-OCT showed serous macular detachment and CME. The patient was treated with oral Methyl prednisolone and intravitreal anti-VEGF inhibitor, with the improvement of findings	The authors state that the timing of ocular involvement points to an immune complex deposition causing vascular occlusion. Response to steroids also bolsters this hypothesis
7	Walinjkar *et al*.[23]	Case report (India)	17-year-old female	Fundoscopy showed a picture of CRVO and macular edema. She was positive for COVID-19 Ig. Investigations revealed no other underlying cause	The authors suggest that the retina may be involved as part of the thromboembolic phenomena accompanying COVID-19 disease
8	Gaba *et al*.[24]	Case report	40-year-old man (UAE)	Indirect ophthalmoscopy showed findings of bilateral CRVO. He was treated with low-molecular-weight heparin	The authors suggest that early anticoagulation should be instituted in severe COVID-19 disease, especially those with other concomitant risk factors, to prevent vaso-occlusive phenomena
9	Monferrer-Adsuara *et al*.[25]	Case report (Spain)	59-year-old woman	The patient had a 7-day history of bilateral blurred vision, 7 days before onset of COVID symptoms. Fundus examination revealed venous stasis and dot blot hemorrhages, which improved with improvement in general condition of the patient	The findings probably represent a coagulopathy-like picture caused by the COVID-19 infection
10	Ortiz-Seller *et al*.[25]	Case report (Spain)	51-year-old female patient	Examination revealed recent-onset multifocal chorioretinitis and bilateral Adie's pupils. The retinal lesions improved with oral prednisolone ophthalmoscopically and on imaging	The authors felt that the COVID-19 virus was responsible for the inflammatory chorioretinitis and Adie's syndrome. Adie's syndrome probably points to the neurotropism of the COVID virus
11	Zago Filho *et al*.[26]	Case report (Brazil)	57-year-old woman	There was Grade 1 vitritis; fundus imaging showed yellowish macular lesions	A diagnosis of outer retinal inflammation and vitritis was made, and other causes of the same were ruled out
12	Benito-Pascual *et al*.[27]	Case report (Spain)	60-year-old woman	Patient had a 2-week history of follicular conjunctivitis followed by panuveitis. Ocular symptoms improved as the patient's systemic condition improved; however, disc pallor was noted	The choroid, neural, and vascular endothelium have ACE2 receptors and represent potential sites of COVID infection

COVID-19 – Coronavirus disease 2019, ACE2 – Angiotensin-converting enzyme 2, CRVO – Central retinal vein occlusion, BRVO – Branch retinal vein occlusion, Hemi-RVO – Hemiretinal vein occlusion, OCT – Optical coherence tomography, SD-OCT – Spectral-domain OCT, CME – Cystoid macular edema, VEGF – Vascular endothelial growth factor, AMN – Acute macular neuroretinopathy, PAMM – Paracentral acute middle maculopathy, OCTA – OCT angiography, RNFL – Retinal nerve fiber layer, SRCP – Superficial retinal capillary plexus

microhemorrhages, and all patients showed hypererflective lesions at the level of the ganglion cell layer and inner plexiform layer, most prominent in the area of the papillomacular bundle. Similar lesions have been noted in animal studies as well. However, there were questions about whether these lesions could be the effect of acute hypoxia or could represent normal retinal vessels.[34,35] However, Marinho *et al*. stood by their findings and said that the lesions showed the absence of blood flow (by B scan overlay of OCTA) and thus were unlikely to be normal retinal blood vessels.[36]

There were three case reports of COVID-19 patients presenting with scotomata in patients recovering from COVID-19 infections, ranging from 8 to 17 days postinfection. Virgo and Mohamed described two Caucasian patients in their thirties who recovered from COVID-19.[19] In the first patient, there was a focal area of hyperreflective change in inner and outer plexiform layers with inner nuclear layer volume loss on OCT, leading to a diagnosis of paracentral acute middle maculopathy (PAMM). The OCT of the other patient showed a focal zone of faint outer plexiform layer hyperreflective change and disruption of the interdigitation zone, making a diagnosis of acute macular neuroretinopathy (AMN). Gascon *et al*. reported a case of a 53-year-old Frenchman whose fundus showed retinal hemorrhages and Roth's spots and OCT showed a picture resembling AMN and PAMM.[17] Gonzalez-Lopez *et al*. reported a case of a 50-year-old patient with fundus findings of peripapillary cotton wool spots in both eyes.[18] OCT showed Retinal nerve fibre layer (RNFL) edema and disruption of the normal reflectivity of the nuclear and plexiform layers in the largest lesion. OCTA showed decreased SCP flow, and automated perimetry showed an arcuate scotoma corresponding to the largest lesion. All these reports again highlight the microvascular damage seen in COVID-19 disease, which may also be seen in other organ systems.

There were six case reports of involvement of the retinal venous system in COVID infection. The first report was that of a 40-year-old man presenting after 6 weeks of COVID infection with decreased vision sensitivity in one eye.[20] Ocular examination revealed a picture resembling papillophlebitis with dilated and tortuous retinal blood vessels, disc edema, macular edema, and hemorrhages, which responded to intravitreal dexamethasone injection. Invernizzi *et al*. reported a case of a 54-year-old man presenting 10 days post-COVID with a unilateral scotoma and defective vision.[21] Fundoscopy and imaging showed retinal hemorrhages and whitening and a fernlike pattern was seen on autofluorescence, which was typical of impending CRVO. There were two case reports of venous occlusion in COVID-19 patients from India, one of which was an inferior hemi-RVO with a superonasal BRVO and the other patient had a CRVO.[22,23] Both cases had associated macular edema and responded to intravitreal anti-VEGF injections. There were two case reports of a bilateral CRVO like picture.[24] The retinal findings improved with improvement of the patients' general condition. In all these cases, it is thought that the inflammation and hypercoagulability as part of COVID-19 disease could play a role in pathogenesis of the vasocclusive events. The COVID-19 associated cytokine storm and hyperinflammatory response could result in a cascade of events which can lead to vascular occlusions. Especially in patients with preexisting risk factors and severe COVID-19 disease, it may be prudent to start early anticoagulation to prevent end-organ, including retinal damage.[24,37] There were three case reports of unique posterior segment manifestations in COVID-19 patients. Ortiz-Seller *et al*. reported a case of multifocal chorioretinitis and bilateral Adie's pupil in a COVID-19 patient presenting with retroocular pain and defective reading 2 days after COVID onset.[26] There were multiple bilateral white-yellowish placoid lesions in the mid-peripheral and posterior retina, which improved with oral prednisolone. The virus was presumed to be responsible for the denervation of the postganglionic pupillary and ciliary muscle nerve supply, resulting in Adie's pupil and providing evidence for the neurotropism of the SARS CoV2 virus. Zago Filho *et al*. described a case of a 57-year-old woman with bilateral red eyes seen 12 days after a COVID 19 symptom onset and diagnosis.[27] A diagnosis of vitritis and outer retinal inflammation was made. The authors hypothesized that these lesions were due to COVID-19 infection and anticipated more reports as the pandemic progresses. Benito-Pascual *et al*. reported a case of a patient who presented with ocular pain, blurred vision and redness in one eye with a 2-week past history of respiratory infection and sinusitis.[28] The patient had a 2-week history of follicular conjunctivitis followed by panuveitis. Other causes of panuveitis were ruled out. Ocular symptoms improved as the patient's systemic condition improved; however, disc pallor was noted. The authors postulated that the choroid has ACE2 receptors which could present a site for virus dwelling and replication.

CONCLUSION

It has been proven beyond doubt that the SARS CoV2 virus can affect the retina. Increasing amounts of evidence to the same have been accumulating as the pandemic progresses. Retinal manifestations are ubiquitous, but microangiopathy and vascular occlusions are among the most common. They probably are a reflection of the severity of the disease and may serve as an indicator of similar events in other organs.

Retinal involvement in COVID can affect vision permanently, and it is therefore very important to safely examine the retina of any COVID-19 patient presenting with new onset visual symptoms by either ophthalmoscopy or retinal imaging. It is anticipated that with time, newer retinal manifestations of COVID-19 disease will be discovered, and there will also be more information about the ones we already know. The ophthalmologist during the time of the pandemic should keep thus his eyes open to the possibility of the SARS CoV2 virus affecting every part of the eye and identifying unknown and hitherto undiscovered manifestations of the disease. As the vaccine is now within reach and with increasing knowledge about the virus, the sense of panic and fear among populations may abate. However, it is best to take care, stay safe, and practice hand hygiene and social distancing to face this challenging situation.

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Conflicts of interest

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Design and development of objective questionnaires

ABSTRACT

Measurements are a fundamental concept in healthcare. Questionnaires are integral to healthcare research and provide healthcare practitioners with objective tools for measurement of several aspects of health care. Questionnaires are developed based on certain contexts and validated for further use in larger populations. The primary goal of questionnaires is to provide valid measures of underlying constructs. The use of inappropriate questionnaires or poorly designed questionnaires affects the quality of data collected and the validity of the study. In this manuscript, we describe issues related to the design and development of questionnaires. These include conceptualization of target constructs and development of item pools, the basic principles of writing the items, formats and derivative versions of questionnaires, and translations. In the second part of this series, we will describe the concepts and process for validation of questionnaires.

Keywords: Construct, measurement, questionnaire development, scale development, test

Questionnaires are often used to collect information on several aspects of healthcare including knowledge, behaviors, attitudes, quality of life, and clinical aspects. Poorly designed and poorly developed questionnaires lead to the collection of poor-quality data that inevitably lead to misleading or wrong conclusions. Information from questionnaires often translates to actions that may impact upon clinical course or practices. Naturally, tests of hypothesized relations between theory-based constructs and their observable manifestations are essential during the development of the questionnaire to establish its validity.[1,2] Validity relates to the interpretation of questionnaires and describes the support provided by the evidence and theory underpinning the development of a questionnaire to interpret test scores and use the questionnaire.[1,2] Establishing the validity of a questionnaire becomes important as the quality of these decisions are driven partly by the quality of information derived from the questionnaires.

Questionnaires validated for use in several populations or globally are available for several health care domains. However, as medical practice and sickness profiles evolve rapidly, it may not be possible to have a previously validated questionnaire for every aspect of healthcare. Questionnaires must be developed from scratch to obtain valid information about a new domain. The selection of several questions from other questionnaires or grouping of several questions does not create a questionnaire. The development of questionnaires involves a systematic process that can establish good construct validity and provide accurate information.

DEVELOPING QUESTIONNAIRES

An initial step in the development of a questionnaire is to form a clear, specific idea of the conceptual model for the questionnaire. The writing of a precise statement with reasonable detail of the target construct is the first step. A new construct should either provide significant improvements over an existing questionnaire or complete a gap in the existing questionnaire. The next step is a detailed literature review that focuses on two elements- (a) are there already existing, validated questionnaires for similar constructs, and (b) to acquire enough knowledge that helps

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to understand the theoretical context of the questionnaire and to differentiate it from other similar constructs. The literature review focuses on the existing construct of interest, related constructs, and constructs that correlate either positively or negatively-with the construct of interest. For example, a construct of satisfaction may relate or correlate with depression, anxiety, stress, guilt, shame, fear, hope, etc. The literature review helps to specify the construct of interest and identify what the construct is, and equally important, what it is not.

The use of standardized, validated questionnaires that can compare results across multiple studies and populations is common in healthcare. The use of questionnaires across populations presume that the questionnaires must elicit comparable, valid results in all sampling frames and retain the context in which the questionnaire was developed.[3-8] However, the validity of questionnaires must be rechecked as contexts and responses may differ between and within populations. A reliable questionnaire yields consistent results across repeated samples and different studies over time.[2] A standardized questionnaire is a written document administered such that the same precise questions are asked to all participants, in the same way, with responses recorded uniformly.[2] Standardizing increases the reliability of the questionnaire. The literature review helps to understand the contextual basis for the development of the original questionnaire, its validity, reliability, and standardization in multiple settings, and to determine if the questions still retain significance in the context of the population to which the questionnaire is proposed to be administered.

ITEM POOLS

The writing of the items in the questionnaire is the next important step. Item writing specifically aims to systematically include content that is possibly relevant and can increase the overall content validity of the questionnaire. A key element to item writing is a good understanding of the theoretical constructs and the major content areas of the questionnaire that is under development. We recommend starting with a larger pool of items across the breadth of the construct as it is easier to delete items than add them later. A larger pool of items allows for an adequate sample of questions pertinent to each content area. The creation of homogeneous subscales, also known as item composites or factored item dimensions, can be used to assess each content area.[9,10] An empirical evaluation of questions added is essential as the questionnaire is developed.[9,11,12] The development of a good questionnaire is an iterative process with repeated assessments of the conceptual basis and psychometric properties of each question in the construct. The repeated analysis during development may reveal that subscales are necessary, that certain content areas may need more questions, that questions must be rewritten, or that questions must be deleted or added for better content validity.

The specific wording of the questions is important. The responses to questionnaires depend on the ability of the respondent as well and physical, cognitive, mental, social, and linguistic elements must be considered.[13] Use simple, clear, and precise language at a reading level that can be understood by many, avoiding slang and colloquialisms, and preferably focused on a single characteristic. It is preferable to avoid words such as commonly, regularly, and frequently.

The choice of format to present the questions is a factor that can influence responses. Two common response formats used in healthcare are the dichotomous (example: yes/no) and the Likert type of rating scales with three or more response options. Other response formats that are used include checklists (these are prone to response bias[14]) and the visual analog or sliding scales that are almost such as numerical rating scales.[15] The format of the question responses can constrain the responses that are possible, and hence it is necessary to consider the response formats very carefully.[9]

Derivative versions of questionnaires, including short-form questionnaires, translations, and age group adaptations are sometimes necessary. Any derivative version must be revalidated before administration. The derivation of short forms does not imply simply the removal of certain items across all or some content areas. Shortening of questionnaires must maintain test information even while reducing the number of questions in a scale. The use of item response theory analytic methods is useful to shorten forms retaining the validity of the questionnaire.[16-19] Translations of validated questionnaires are often used. It is important to revalidate the translated versions before administration. Translations are usually done through a two-way process with translation from English to the regional language as the first step and a back translation from the regional to English as the second step. The ability of the questionnaire to retain the original contextual meaning is assessed and the construct validity of the questionnaire is reassessed. However, the effects of acculturation and the impact of language on cultural frames must be considered carefully.[20] It is preferable not to use translated questionnaires if the construct validity of the translated version is not provided. This is an important consideration as Universities and Boards in India require healthcare students in India to use translated versions of

validated questionnaires (if a questionnaire is used) as part of the mandatory student dissertation experience.

Another area of concern is the use of questionnaires across age groups. The questionnaires must be adapted and revalidated for use across ae groups. Thus, a questionnaire developed for use in an adult population must not be used for an adolescent or pediatric population without validation. These adaptations can be complex as parents may be respondents when questionnaires are administered to small children. There can be multi-sourced assessments (parents, teachers, nurses, etc) and questionnaires may be supplemented with behavioral observations.[21-23] The influences of developmental changes on constructs and response to constructs including a possible cognitive decline in the aged must be considered.[23]

Careful consideration must be given to the layout of the questions. The questionnaire must be in an adequately sized font, easy to read format, and with adequate spacing. Considerations at the development stage must include data analysis plans including the time, resources, and expertise for analysis. For instance, if you are designing a questionnaire with open-ended questions, you must be aware of or have support for the analysis of open-ended questions.

In conclusion, the use of questionnaires in healthcare research is routine practice. The development of a validated questionnaire is a systematic process that involves several steps and repeated analysis of the psychometric properties of the questionnaire. It is important to understand and provide due respect to the process of development of a questionnaire before it is used or adapted or translated for use. In the next part of this series, we will look at the process of validating questionnaires.

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There are no conflicts of interest.

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Original Article

Clinical profile and outcomes of ophthalmia nodosa in South India: A retrospective study

ABSTRACT

Aim: The aim of the study was to report the clinical presentation, course, and final outcomes of ophthalmia nodosa and create awareness among general ophthalmologists regarding the disease. **Materials and Methods:** A retrospective analysis of the cases of ophthalmia nodosa was carried out from January 2018 to December 2018. Ninety-eight eyes were included in the study. **Results:** Patients presented with redness (76.53%), foreign-body sensation (61.91%), pain (48.98%), lacrimation (28.57%), and photophobia (7.14%). Hairs were found in the conjunctiva in 63.26%, cornea in 39.80%, anterior chamber in 4.08%, lens in 3.06%, and vitreous in 8.16%. Patients with anterior segment involvement responded well to treatment, which included caterpillar hair removal, topical steroids, and cycloplegics. Patients with retinal exudates responded to therapy which included systemic antibiotics and steroids. Multiple sittings of hair removal were required in 38.78% of patients. Follow-up of the patients ranged from a minimum of 30 days to a maximum of 180 days. **Conclusion:** Ophthalmia nodosa is a relatively common condition in this part of the world. It has a good outcome when timely diagnosed and appropriately managed.

Keywords: Caterpillar hair, inflammation, ophthalmia nodosa

INTRODUCTION

Ophthalmia nodosa is an inflammatory response of ocular tissue due to caterpillar (CP) hair or other insect hair and few plant hair that come in contact with the eye. Ocular inflammation is likely due to locomotion and toxin secreted by the venom gland connected to the hair shaft.[1,2] Ocular presentation of the disease varies according to the location of the CP hair. It may range from a local toxic reaction, keratoconjunctivitis, or conjunctival nodules, to severe manifestations such as iritis, vitritis, papillitis, and endophthalmitis.[3]

Ophthalmia nodosa is a seasonal disease, and is seen more often in coastal regions. It is usually in an innocuous condition and responds well to conservative management. Intraocular penetration of CP hair is seen in few patients, which might lead to devastating complications, requiring a surgical treatment.

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The aim of our study was to report the clinical presentation, course, and final outcomes of ophthalmia nodosa and create awareness among general ophthalmologists for its timely and appropriate management.

MATERIALS AND METHODS

A retrospective review of hospital records was performed between January 2018 and December 2018. One hundred and twenty-five patients were diagnosed to have ophthalmia nodosa, out of which, 27 had a follow-up of <30 days and, hence, were excluded from the study. Ninety-eight eyes

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were included in the study. A comprehensive ophthalmic examination, including best-corrected visual acuity, intraocular pressure with applanation tonometry, slit-lamp examination, and indirect ophthalmoscopy, was performed for each case. Pediatric patients were evaluated under general anesthesia.

CP hairs from conjunctiva were removed using a suture tying forceps, and those in deep conjunctiva, or corneal stroma, were removed with a 26G hypodermic needle under topical anesthesia. The deep stromal hairs were not removed, as removal would have caused significant corneal scarring and that these hairs are often inert.

Medical treatment included topical lubricant and antibiotic drops. Steroids and mydriatic eye drops were added in cases with anterior uveitis. Systemic steroids were initiated when the posterior segment was involved. During subsequent follow-up visits, patients were reexamined for hair and their subsequent removal.

The study was approved by the institutional review board and adhered to the tenets of the Declaration of Helsinki.

RESULTS

A total of 98 patients with ophthalmia nodosa were included in the study, out of these, 53 (54.08%) were male and 45 (45.92%) were female. The age of the patients ranged from 7 months to 67 years. All the cases were unilateral. Majority of the patients (76) had a history suggesting contact with an insect, and the rest of the patients (22) had a history of dust fall. Among them, 28 patients (28.57%) were working in fields, 20 patients (20.41%) were driving a two-wheeler, and 7 patients (7.14%) were sitting under trees and the rest could not give a specific history.

Majority of the cases in our study occurred in the month of March (14), closely followed by April (12). Month-wise distribution is shown in bar graph [Figure 1].

Majority of the patients presented with redness (76.53%), foreign-body sensation (61.91%), pain (48.98%), lacrimation (28.57%), and photophobia (7.14%). The duration of symptoms varied from 1 day to 60 days. At presentation, visual acuity ranged from 20/20 to 20/30 in 69 patients (70.41%), 20/40 to 20/120 in 18 patients (18.37%), and <20/120 in 2 patients (2.04%).

CP hairs were seen in the anterior segment in the majority of the patients, whereas vitreous involvement was seen only in eight eyes (8.16%). Hairs were found in the conjunctiva in

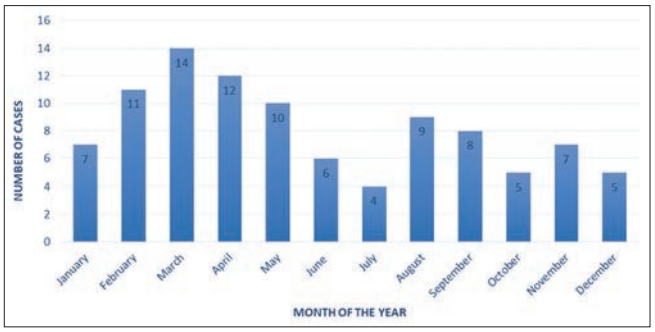


Figure 1: A bar graph illustrating month-wise distribution of cases in our study

62 eyes (63.26%), cornea in 39 eyes (39.80%), and anterior chamber (AC) in 4 eyes (4.08%). Lens involvement was seen in three patients (3.06%) where the CP hair was lodged in the anterior lens capsule.

The conjunctival signs included congestion in 75 patients (76.53%), CP hair in the upper tarsal conjunctiva in 35 patients (35.71%), hair in the lower tarsal conjunctiva in 27 patients (27.55%), papillary reaction in 11 patients (11.22%), and membrane on the upper tarsal conjunctiva in 3 patients (3.06%). Pattern abrasions were seen in 84 patients (85.71%), superficial punctate keratopathy was seen in 17 patients (17.35%), epithelial defect was seen in 21 patients (21.43%), and infiltrates were seen in 3 patients (3.06%). AC reaction or iridocyclitis was seen in 12 patients (12.24%) and iris granulomas were seen in five patients (5.10%). Vitreous haze was seen in three patients (3.06%) and snowballs and retinal exudates were seen in two patients (2.04%), wherein systemic antibiotics were given in addition to systemic and topical steroids.

Multiple sittings of hair removal (range: 2–5 sittings) were required in 38 patients (38.78%). The follow-up of the patients ranged from a minimum of 30 days to a maximum follow-up of 180 days. At the last follow-up, minimal conjunctival congestion was seen in 19 patients (19.39%), corneal scarring in eight patients (8.16%), CP hair in the deep stroma in 22 patients (22.45%) [Figure 2], and punctate epithelial erosions in 16 patients (16.33%). AC reaction in the form of occasional cells and 1+ flare was seen in four patients (4.08%). The vitreous cavity showed CP hair in eight patients (8.16%) without any signs of inflammation. Visual acuity was 20/20–20/30 in all except six patients, out of which, five had cataracts and the remaining patient had leukomatous corneal scar.

Hair isolated from the conjunctiva was studied randomly under a light microscope at ×4 and ×40 magnification, which revealed a smooth shaft without spines [Figure 3a and b].

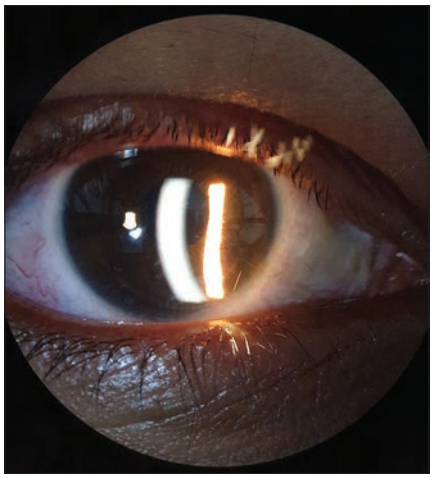


Figure 2: Slit-lamp image showing retained deep stromal setae with minimal surrounding congestion

DISCUSSION

Schon published the first report of this condition in 1861.[4] The spectrum of clinical manifestations was designated as "ophthalmia nodosa" by Pagenstecher in 1883.[5] It was referred to as "pseudotuberculoma" by Wagenmann in 1890 and "pseudotrachoma" by Schmidt Rimpler in 1899. Saemisch coined the term "ophthalmia nodosa" in 1904.[6]

The first case reported from India was as late as 1968,[7] and is still underdiagnosed due to lack of awareness among general ophthalmologists. Hence, this study was conducted to highlight the clinical manifestations of ophthalmia nodosa, its management, and creating awareness among ophthalmologists for a timely diagnosis and immediate CP hair removal, avoiding untoward complication.

A seasonal variation was found in the presentation of ophthalmia nodosa in our study, as a majority of cases occurred from February to May. This finding is in contrast to other Indian studies where a majority of cases are reported to occur from July to September,[8] whereas, in the Western world, most of the cases are reported in December and January, as it is the time for harvesting of hay and the time of greatest CP activity.[5]

Caterpillar setae can be found in the eye due to contact with caterpillars, exposure to larval cocoon having shed setae or direct entry of wind-borne setae.[9] The various manifestations of ophthalmia nodosa include toxicity and locomotory effects of the setae. Toxin originates in the venom gland connected to the hair shaft, which is transferred through the hollow shaft. Penetration of lids and ocular surface by setae is aided by muscular contraction of the lid muscles and rubbing of lids in response to irritation caused by the toxin. Intraocular

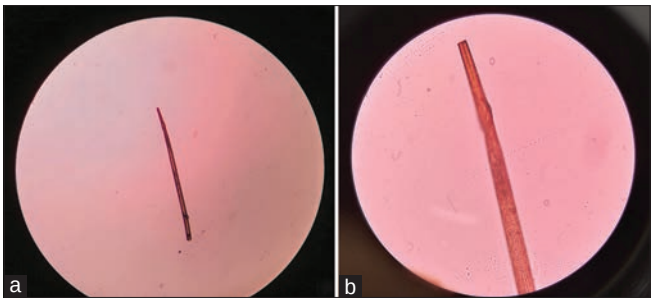


Figure 3: Light microscopic image of setae with no spine along the shaft at, (a) (×4) (b) (×40)

penetration is very rare. Gundersen *et al*. postulated that setae do not have a propulsive power and are propelled further as a result of globe movements and iris pulsations.[10] Ashcher observed that the inflammatory exudates against the broken end of the hair pushed it to move along the path of least resistance.[11]

Duke-Elder and MacFaul described that after the initial symptoms of trauma, there was a quiescent interval of usually 3–5 days, followed by a recurrence of symptoms.[12] However, we found a latent period of <24 h in all our cases, as in other Indian case reports. This difference has been attributed to the type of CP hair by Sethi and Dwivedi.[8] Most of the Western articles reported barbed hair in their cases in contrast to the smooth and nonbarbed hair in India.

CP setae-incited inflammatory reaction has been classified into the following five types by Cadera *et al*.:[3]

- Type 1: An acute reaction to the hair consisting of chemosis and inflammation. This begins immediately and lasts for some weeks
- Type 2: Chronic mechanical keratoconjunctivitis caused by hair lodged in the bulbar or palpebral conjunctiva. Foreign-body sensation occurs, and linear corneal abrasions are seen
- Type 3: Formation of gray–yellow nodules in the conjunctiva (granulomas). Setae may be subconjunctival or intracorneal and may be asymptomatic
- Type 4: Iritis secondary to hair penetration of the anterior segment
- Type 5: Vitreoretinal involvement (10%–20%) after hair penetrates the posterior segment through the AC or transscleral route. This may occur early or some years later. Mild vitritis or vitreous haze is commonly reported as seen in three patients in our series, whereas frank endophthalmitis is very rare.

There are different schools of thought regarding the management of deep-seated CP hair; one school of thought opines that they should be observed as manipulation leads

to inflammation and scarring,[13] while the other imparts that these might penetrate deeper and inflammation is more likely and difficult to control.[14-16] We followed the first school of thought, and CP hairs in deep stroma, AC, or vitreous were left untreated without any inflammation at a later date.

Fraser *et al*. suggested argon or Nd-YAG laser as the modality of treatment of ophthalmia nodosa as it neutralizes the toxic effects of intraocular setae.[17] However, there is limited evidence to support it as a treatment modality.

To summarize, ophthalmia nodosa is a common entity in the southern part of India. It has a varied presentation, ranging from mild conjunctivitis to rarely frank endophthalmitis. It could be easily missed by an ophthalmologist unless he/she is aware of the disease entity. Timely diagnosis and appropriate treatment, including CP hair removal, results in a good prognosis. Importance of follow-ups should be stressed upon to the patients as many of them require multiple sittings of hair removal. Awareness should be raised regarding the wearing of protective glasses/helmets while driving a two-wheeler or working in fields.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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Original Article

Prevalence of subclinical keratoconus in children presenting with refractive errors: A cross-sectional study

ABSTRACT

Background: Keratoconus is a progressive noninflammatory condition that often starts to develop at the age of puberty. The subclinical disease remains unexplored geographically for its prevalence in children. This study was aimed to determine the prevalence of subclinical keratoconus in children presenting with refractive errors. **Methods:** A cross-sectional study was conducted among children (below 14 years of age) with refractive errors. Corneal topography indices such as Belin/Ambrosio enhanced ectasia total deviation value (BAD_D), index of vertical asymmetry (IVA), and index of surface variance (ISV) of both eyes were selected from the medical records. The prevalence of subclinical keratoconus was identified using the parameters BAD_D = 1.54–2.38, IVA >0.14, and ISV >22. The incidence was calculated and statistically analyzed. **Results:** Total 726 eyes (354 right and 372 left eyes) from 363 children (190 males and 173 females) were included in the study. Among the total 726 eyes studied, 132/726 (18.18%) showed subclinical keratoconus with 58/132 (43.93%) in right eyes and 74/132 (53.06) in left eyes (P = 0.3411). Definite keratoconus was observed in total 37/726 eyes only (5.09%) with 23/37 in right eyes (62.16%) and 14/37 left eyes (37.83). No statistically significant (P = 0.1678) difference was found between the incidence of definite or subclinical keratoconus with cases of normal indices. **Conclusion:** The incidence of subclinical keratoconus among children presenting with refractive errors was 18.18%. Corneal topography and tomography may be recommended for children presenting with refractive errors for identifying subclinical keratoconus and to arrest its progression at the onset.

Keywords: Belin/Ambrosio enhanced ectasia total deviation value, corneal topography, index of surface variance, index of vertical asymmetry, keratoconus, mean keratometry

INTRODUCTION

Keratoconus, a bilateral noninflammatory corneal ectatic disorder, often starts to develop at the age of puberty.[1] The condition can aggravate in the third decade of life and thus causes a heavy burden to patients. Thinning of the corneal stroma is found in this noninflammatory disease which may or may not lead to irregular astigmatism. In order to arrest its progression, corneal cross-linking, especially in the early stages, is recommended.[2] Therefore, early diagnosis is of vital importance. When the suggestive clinical signs and symptoms of subclinical keratoconus are overlapping with normal cornea, the diagnosis will be challenging for ophthalmologists.[3] Rabinowitz *et al*.[4,5] defined keratoconus suspect in a progressive perspective, and their definition was independent of the status of the fellow eye as no slit-lamp findings, asymmetric bow tie pattern with a skewed radial axis on videokeratography, or no scissoring on retinoscopy.

A combination of pachymetric, topometric, and aberrometric indices was used to differentiate subclinical from normal

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cases.[3] Belin/Ambrosio Deviation Display (BAD_D), index of vertical asymmetry (IVA), and index of surface variance (ISV) were the best variables for the diagnosis of subclinical keratoconus. BAD_D and mean keratometry were the criteria for the diagnosis of definite keratoconus.[3] Keratoconus affects all races. However, very little information is available on the relative frequency of its incidence in patients of different ethnic origins.[6] A previous review on keratoconus by Kok *et al*. concluded that the prevalence of the disease among Indians is at an earlier onset.[7] Despite the incidence of keratoconus among the Indian children, data on the subclinical form of this disease is lacking. Hence, this study was aimed to evaluate the prevalence of subclinical keratoconus among children presenting with refractive errors which may help to prevent the progression of the disease at an early stage.

METHODS

Study design

A cross-sectional study was conducted in the department of ophthalmology during the period of January 2018 to February 2020. The children below the age of 14 years presenting with unilateral or bilateral refractive errors and uncorrected visual acuity of <6/6 in at least one eye were included in the study. A thorough clinical examination was done in all the children. Cases with complete details such as age, gender, and corneal topography indices were selected from medical records. Cases with astigmatism (0.5–5 diopters) were categorized as simple myopia-hypermetropia, compound myopia-hypermetropia, and mixed astigmatism. Children of age above 14 years, those with incomplete data, and cases with history of corneal surgery or corneal scarring and contact lens users were excluded from the study. Informed consent was obtained from the parent or guardian for selecting their data for the study. The study was conducted according to the Helsinki Declaration, 1975, as revised in 2000 and approved by the Institutional Ethics Committee.

Study procedure

Examination was conducted using WaveLight Oculyzer II and 25 single Scheimpflug images which were taken from each eye. BAD_D, IVA, and ISV were identified as the best diagnostic criteria for the diagnosis of subclinical keratoconus. The data were extracted to a Microsoft Excel sheet. The value of BAD-D ≥1.54 (but ≤2.38), IVA >0.14, and ISV >22 was used to identify the subclinical keratoconus, while BAD-D >2.38 with K mean ≥44.9 was selected to diagnose the definite keratoconus.[3] The prevalence of subclinical keratoconus was identified among the total cases and presented as percent incidence. Furthermore, the prevalence of definite keratoconus was also analyzed.

Statistical analysis

All the parametric data were presented as mean ± standard deviation (SD). The nonparametric data were presented as a percentage. Student *t*-test was used to find the statistically significant difference among the parametric data (SPSS, 16 v, IBM, CA, USA (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc)), while Chi-square test was used to find the significant difference between SKC (subclinical keratoconus) and normal topographic indices. $P < 0.05$ was considered statistically significant.

RESULTS

Total 726 eyes (354 right and 372 left eyes) from 363 children (190 males and 173 females) of age between 3 and 14 years were included in the study. The mean age was 9.01 ± 2.61 years, with an average age of 8.52 ± 2.52 years in male children and 8.65 ± 2.70 years in female children. No significant difference was found between the ages of male and female children ($P > 0.05$, Student's *t*-test). Simple myopic astigmatism was found in a total of 157/726 eyes (21.62%), which was the prevalent refractive error, followed by compound myopic astigmatism (71/726; 9.77%). Normal topographic indices were observed in 557 eyes (75.40%) with 273 right eyes (49.01%) and 284 left eyes (50.98%). Among the total 726 eyes studied, 132/726 (18.18%) showed subclinical keratoconus with 58/132 (43.93%) in right eyes and 74/132 (53.06) in left eyes [Table 1]. No statistically significant (Chi-square value 0.9064; $P = 0.3411$) difference was found between the incidence of subclinical keratoconus in right and left eyes with that of right and left eye normal topographic indices.

Among the total subclinical keratoconus obtained, the prevalence of simple myopic astigmatism was found in total 83/132 eyes (62.87%) with 35/83 (42.16%) in right eyes and 48/83 (57.83%) in left eyes. The simple myopic astigmatism was found in 24 eyes and compound myopic astigmatism found in 6 eyes. No cases of simple hypermetropia, simple hypermetropic astigmatism, or simple myopia were observed in these subclinical cases

Definite keratoconus was observed in total 37/726 eyes only (5.09%) with 23/37 in right eyes (62.16%) and 14/37 in left eyes (37.83). No statistically significant (Chi-square value 1.903; $P = 0.1678$) difference was found between the incidence of definite keratoconus in right and left eyes with that of right and left eyes of cases with normal topographic indices. Among the total definite keratoconus obtained, the prevalence of simple myopic astigmatism was found in total 24/37 (64.86%) eyes with 13/24 (54.16%) in right eyes and 11/24 (45.83%) in left eyes. No evidence of simple

Table 1: Distribution of subclinical keratoconus with various astigmatism and myopia among children with refractive errors

Condition (%)	R/L (%)	SMA (%)	CMA (%)	MA (%)	CHA (%)	SH (%)	SHA (%)	SM (%)	E (%)
SKC (*n*=132; 18.18)	R=58 (43.93)	35 (42.16)	11 (45.83)	10 (50.00)	1 (50.00)	1 (33.33)	0	0	0
	L=74 (53.06)	48 (57.83)	13 (54.16)	10 (50.00)	1 (50.00)	2(66.66)	0	0	0
	Total=132	83 (62.87)	24 (18.18)	20 (15.15)	2(1.51)	3(2.27)	0	0	0
DK (*n*=37; 5.09)	R=23 (62.16)	13 (54.16)	5 (83.33)	4 (66.66)	1 (100.00)	0	0	0	0
	L=14 (37.83)	11 (45.83)	1(16.66)	2 (33.33)	0 (0)	0	0	0	0
	Total=37	24 (64.86)	6 (16.21)	6 (16.21)	1 (2.7)	0	0	0	0
Normal topographic indices (*n*=557; 75.40)	R=273 (49.01)	141 (52.80)	67 (52.75)	28 (62.22)	1 (33.33)	2(4.76)	6 (42.85)	12 (63.15)	16 (40.00)
	L=284 (50.98)	126 (47.19)	60 (47.24)	17 (37.77)	2 (66.67)	(95.23)	8 (57.14)	7 (36.84)	24 (60.00)
	Total=557	267 (51.54)	127 (22.80)	45 (8.07)	3 (0.53)	42 (7.54)	14 (2.51)	19 (3.41)	40 (7.18)
Total	726	374 (51.51)	157 (21.62)	71(9.77)	6(0.82)	45(6.19)	14 (1.92)	19 (2.61)	40 (5.50)

P=0.050 (χ^2=3.85), significant difference found between SKC and KC. P=0.3411(χ^2=0.9064), no significant difference found between the incidence of subclinical keratoconus in right and left eyes with that of right and left eye normal topographic indices. SKC: Subclinical keratoconus; KC: Definite keratoconus; R: Right eye; L: Left eye; SMA: Simple myopic astigmatism; CMA: Compound myopic astigmatism; MA: Mixed astigmatism; CHA: Compound hyperopic astigmatism; SH: Simple hypermetropia; SHA: Simple hypermetropic astigmatism; SM: Simple myopia; E: Emmetropia

hypermetropia, simple hypermetropic astigmatism, or simple myopia was found among children with definite keratoconus

Among the total eyes, 557/726 (75.40%) eyes with refractive errors were found with normal indices, 273/557 (49.01%) in right eyes and 284/557 (50.98%) in left eyes. The prevalence of simple myopic astigmatism was found in total 267/557 eyes (51.54%), 141/267 (52.80%) in right eyes and 126/267 (47.19%) in left eyes. In this group with normal indices, total compound myopic astigmatism was found in 127/557 (22.80%), mixed astigmatism in 45/557 (8.07%), compound hyperopic astigmatism in 3/557 (0.53%), simple hypermetropia in 42/557 (7.54%), simple hypermetropic astigmatism in 14/557 (2.51%), simple myopia in 19/557 (3.41%), and emmetropia in 40/557 (7.18%).

DISCUSSION

The diagnosis of subclinical keratoconus remains a challenge to ophthalmologists due to the overlapping of many topographic indices with the normal cases. We have taken the Pentacam indices with acceptable specificity and sensitivity to identify subclinical cases. Studies suggest that removing the data of central 3.5 mm height and the use of enhanced best fit sphere instead of the standard mode in calculating BAD_D will be a more sensitive and specific index for detecting subclinical keratoconus. Pentacam top indices are used for diagnosing subclinical and definite keratoconus.[3]

In BAD_D, a reference surface was defined based on the individual's own cornea after excluding the conical orectactic region (keratoconus/ectasia detection with the Oculus Pentacam; Belin/Ambrosio enhanced ectasia display).[5] The enhanced BFS, while further exaggerating the conical protrusion, closely approximates the more normal peripheral cornea. This method in calculating BAD_D is an even more sensitive and specific index to detect subclinical keratoconus. ISV is the unitless SD of individual corneal sagittal radii from the main curvature. ISV is thus an expression of the corneal surface irregularity.[8]

It is also elevated in all types of corneal surface irregularities. In our study, corneal scars and contact lens users were excluded from the study. IVA (in mm) is the mean difference between inferior and superior corneal curvatures.[9] IVA is thus the value of curvature symmetry with respect to the horizontal meridian as the axis of reflection.[9] An ISV more than 22 and an IVA more than 0.14 are taken as keratoconus suspects along the lines of research by Hashemi *et al*.[3] According to Hashemi *et al*., ISV and IVA indices had better predictive power in detecting subclinical keratoconus than other known variables like maximum/mean keratometry.[3] The cutoff value of 45D according to their findings was taken as the cutoff point for definite keratoconus.

The results of this study revealed that 18.18% of children with refractive errors had subclinical keratoconus. The incidence was found to be varying among the population studied. The previous study indicates that keratoconus affects all races and very little information is available in South Indian patients.[6] In this study, we found that the average age of males and females with subclinical keratoconus was 8.5 ± 2.5 and 8.6 ± 2.7 years, respectively. Among the various indices analyzed, BAD_D was found to be more reliable for differentiating subclinical from definite keratoconus; hence, it was used in this study.[10,11] We found the incidence of definite keratoconus in 5.09%. This result is in consistent with the previous report from South India which showed a prevalence of 5.2%,[12] while in Central India, it was reported as 2.3%.[13] No gender-wise difference was noticed in this study like the previous studies.[14,15] However, refractive

errors were more observed in male children than female. Among the errors presented, simple myopic astigmatism was the most prevalent among the total cases.

The disease is found to be progressive until the third or fourth decade of life, and then, it usually arrests.[16] Various risk factors for the incidence of keratoconus were reported previously. Among those, a high rate of incidence was associated with ocular rubbing, ocular allergies, Down's syndrome, and tapetoretinal degeneration, while a lower rate of incidence was found in children with retinitis pigmentosa, Leber's congenital amaurosis, congenital cataract, and diabetes mellitus. The disease showed rapid progression in cases of eye rubbing, atopic eye disease, vernal keratoconjunctivitis, pregnancy, and frequent change of glasses.[12] Among the pediatric patients below 14 years of age with progressive keratoconus, accelerated collagen cross-linking was reported as an effective and safe procedure for the management.[17] However, the published data on the best treatment modality for a particular stage of keratoconus are lacking. Fernández Pérez *et al*. concluded the effectiveness of early diagnosis of keratoconus using highly specific diagnostic equipment to halting the disease at its asymptomatic subclinical stages so as to avoid unnecessary treatments in false-positive cases.[18] Family history of keratoconus was found to be varying.[19] Previous study reported that progression of the disease was seen in 52% of the cases.[12]

Limitations

We did not include the family history of these children and progression of the disease. Small sample size is one of the major limitations of this study. Furthermore, BAD_D, ISV, and IVA aberrometry data were not included in this study. Hence, a multicenter study to support the conclusion is further warranted.

CONCLUSION

Subclinical keratoconus is a less studied subject, especially in children. As far as we know, this is the first study that shows the prevalence of subclinical keratoconus in children with refractive errors in South India. In this study, we have introduced Pentacam indices that have acceptable sensitivity and specificity to identify cases of subclinical and definite keratoconus in children with refractive errors. This study shows the importance of detecting subclinical keratoconus in young children who need to be followed up for the development of a frank keratoconus and also measures can be taken to arrest the development of keratoconus. This study also stresses the importance of close follow-up of children with refractive errors with a corneal topography and tomography.

It is essential to recognize that keratoconus suspect is a topographic classification of an abnormal pattern that resembles keratoconus with no definite characteristics. The study concluded that though the incidence (18.18%) of subclinical keratoconus was statistically nonsignificant, children presenting with refractive errors should be recommended for corneal topography for identification of subclinical keratoconus in order to arrest the progression of the condition at the earliest.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Visual rehabilitation in pediatric cataract with primary intraocular lens implantation

ABSTRACT

Aim: The aim of this study was to show visual rehabilitation in pediatric cataract with primary intraocular lens implantation. **Materials and Methods:** 106 eyes of 91 pediatric patients between 2 to 20 years of age who underwent cataract surgery with primary IOL implantation from June 2018 to January 2020 were included in the study. All the surgeries were performed by a single experienced pediatric ophthalmologist. Phacoemulsification, anterior vitrectomy, and primary posterior capsulorhexis with primary IOL implantation were done in all patients. Patients were reviewed 1 week, 1 month, and 6 months postoperatively. **Results:** Visual acuity improved from 1.7 logarithm of the minimum angle of resolution (logMAR) before the surgery to 0.74 logMAR at the last follow-up. Twelve eyes had postoperative complications which included posterior capsule opacification in 12 eyes, pupillary fibrin membranes in 17 eyes, and corneal edema in 2 eyes. **Conclusion:** The current study suggests that primary IOL implantation is safe when in an experienced hand for pediatric age group.

Keywords: Anterior vitrectomy, pediatric cataract, phacoemulsification, posterior capsulorhexis, visual rehabilitation

INTRODUCTION

Cataracts are an opacified intraocular crystalline lens which is the major cause of blindness in children. The prevalence of childhood cataract in developing countries has been reported as 1–15 cases in 10,000 children. Globally estimated data are of 200000 children blind due to bilateral cataract.[1]

Bilateral congenital cataract can be hereditary with a prevalence of 8.3%–25% of cases, with 75% being autosomal dominant in inheritance.[2] Intrauterine infections such as rubella, herpes simplex virus, and varicella are common causative agents. Mostly, all bilateral congenital cataracts are idiopathic. Few metabolic disorders such as galactosemia and hypocalcemia also have an association with congenital cataract. There also occurs a strong association of congenital cataract with myriads of syndrome such as trisomy 21, Turner, trisomy 31, Lowe syndrome, and Alport syndrome. The optimal time for dense congenital cataract removal is 4–8 weeks of life. If the management is done before 4 weeks, there occurs an increased risk of glaucoma, and if after 8 weeks, there is a risk of compromised visual outcome.[3,4] Management and visual rehabilitation, especially for unilateral cataract, is a daunting task with often disappointing results.

MATERIALS AND METHODS

Clinical records of 112 eyes of 82 patients aged between 2 and 20 years with congenital, traumatic, and developmental cataract who underwent phacoemulsification with primary intraocular lens (IOL) implantation from June 2018 to

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February 2020 at a tertiary eye care center in Central India were retrospectively reviewed.

Medical records were analyzed, and the following data were gathered regarding patients' anterior segment examination and type of cataract, which were further categorized nuclear, zonular, posterior subcapsular, polar, and total.

Preoperative and postoperative visual acuity was assessed using fixation patterns and Snellen's acuity chart in preliterate and literate patients, respectively. Ocular biometry included records of axial length, keratometry, and IOL power calculations using IOL Master (Carl Zeiss Meditec, Germany). Routine investigations and B-scan were done in all patients. All the surgeries were performed single handedly by an expert pediatric surgeon under general anesthesia by phacoemulsification, anterior vitrectomy, and primary posterior capsulorhexis with primary IOL implantation in bag; vitreoretinal backup was called for if required. Any intraoperative and postoperative complications and intraoperative difficulties were noted.

Postoperative day 1 detailed anterior segment examination and posterior segment glow were assessed; all the patients were postoperatively advised topical tobramycin 0.3% eye drops four times a day for a week, atropine sulfate 1% eye ointment bedtime or homatropine 2% eye drops twice a day for 2 weeks, and prednisolone acetate 1% 8–12 times per day with gradual tapering in 6 weeks. Patients were reviewed 1 week, 1 month, and 6 months postoperatively. Patients with other organic ocular diseases such as ocular deviations, retinopathy of prematurity, persistent hyperplastic primary vitreous, anterior segment dysgenesis, and raised IOP and those who failed to follow up till 6 months were excluded.

Data were recorded in Microsoft Excel Sheet (version 12.0, Microsoft, Washington, USA), and percentage, proportions, and frequency were analyzed.

RESULTS

A total of 82 patients were included in the study, with 112 eyes accountable. Of the 82 patients, 8 were traumatic cataract which was excluded from the study. Forty-eight patients had unilateral cataract while 28 had bilateral, 60 eyes of 40 patients had congenital cataract, and 44 eyes of 34 patients had developmental cataract. Forty-four patients (59.45%) were male and 30 patients (40.54%) were female. The mean age at surgery was 69.73 months.

Out of 104 eyes operated, 88 eyes (84.6%) had no postoperative complications and 16 eyes had postoperative complications which included posterior capsule opacification (PCO) in 2 eyes (1.9%), pupillary fibrin and membranes in 10 eyes (9.6%), and corneal edema in 4 eyes (3.8%) [Table 1].

The average mean visual acuity was 1.02 logarithm of the minimum angle of resolution (logMAR) following surgery. Visual acuity gain of 6/12 Snellen's acuity or 0.30 logMAR was considered a good visual prognosis. Twenty-eight eyes both of congenital cataract and developmental cataract, 20 eyes with unilateral cataract, and 40 eyes with bilateral cataract had a good mean visual acuity of 0.27 logMAR, 0.24 logMAR, 0.29 logMAR, and 0.21 logMAR, respectively [Table 2].

The average mean age of operated unilateral cataract patients was 9.3 years and their mean best-corrected visual acuity (BCVA) improved from 1.91 logMAR preoperatively to 0.93 logMAR postoperatively. The mean age of operated bilateral cataract patients was 7.7 years and their mean BCVA improved from 1.62 logMAR preoperatively to 0.88 logMAR postoperatively [Table 3].

Table 1: Eyes with good and poor visual acuity postoperatively in different categorical variants and mean age of patients in both the groups

Factors	Eyes with good visual acuity	Eyes with poor visual acuity
Age at surgery (mean)	68.23 months	71.73 months
Males	26	32
Females	28	18
Congenital cataract	28	32
Developmental cataract	28	16
Unilateral cataract	20	28
Bilateral cataract	40	16

Table 2: Mean visual acuity in eyes with good and poor visual acuity postoperatively in different categorical variants

Variables	Vision in eyes with good visual prognosis (mean) (logMAR)	Vision in eyes with poor visual prognosis (mean) (logMAR)
Congenital cataract (60)	0.27	1.07
Developmental cataract (44)	0.24	0.9
Unilateral cataract (48)	0.29	1.11
Bilateral cataract (56)	0.21	0.8

logMAR – Logarithm minimum angle of resolution

Table 3: Comparison of pre- and postoperative best-corrected visual acuity in unilateral and bilateral cataract

Variables	Mean age (years)	Mean BCVA (logMAR)	
		Preoperative	Postoperative
Unilateral cataract	9.3	1.91	0.93
Bilateral cataract	7.7	1.62	0.88

BCVA – Best-corrected visual acuity, logMAR – Logarithm minimum angle of resolution

The average visual acuity improved from 1.7 logMAR before the surgery to 0.74 logMAR at the last follow-up. BCVA improvement was noticed in 84 eyes (80.7%) at the last follow-up compared with their preoperative measurement. In 20 eyes (19.2%), there was little improvement or no change in visual acuity.

DISCUSSION

The results from this study demonstrate that good outcomes are achievable in children undergoing primary IOL implantation following cataract surgery. More than 80% of the eyes had an improvement in visual acuity and more than 50% of the eyes achieved 6/12 Snellen's acuity or 0.3 logMAR visual acuity at the last follow-up. The complication rate can be compared with that previously reported.[5,6]

Pediatric cataract surgery and aphakia correction after cataract removal presents unique management problems rarely encountered in adult patients. Cataract surgery in children cannot be delayed once a cataract has developed because of the risk of stimulus deprivation amblyopia. With the amblyogenic factor removed, visual development of the operated eye is threatened by anisometropia. Unilateral aphakia correction with glasses produces up to 35% image difference; the use of contact lenses reduces this to 10%. IOL implantation results in aniseikonia of 0%–4%.[7,8]

As the cataract surgery is evolving with the ability to provide early, effective, and constant optical rehabilitation,[9-11] several authors have reported a good vision[12-16] and binocular function[9,11,17-19] in children with unilateral cataract after surgery. Our results showed that 41.6% of children with unilateral cataract who underwent cataract removal and primary IOL implantation between 2 and 20 years of age achieved 0.3 logMAR or better visual acuities, which is a prerequisite for good binocular function. However, good binocular function outcome is limited.

Primary posterior capsulorhexis and anterior vitrectomy are recommended for patients aged 8 years or less.[20] All of our patients underwent anterior vitrectomy and primary posterior capsulorhexis, as strongly recommended in the literature.[21,22] This can explain why only two patients developed PCO.

In our series, primary IOL implantation was performed in all 104 eyes [Figures 1-3]. The mean visual acuity significantly improved from 1.7 logMAR before the surgery to 0.74 logMAR at the last follow-up. Nystagmus and strabismus were present in six eyes of 11.5% of patients before the surgery. It is a

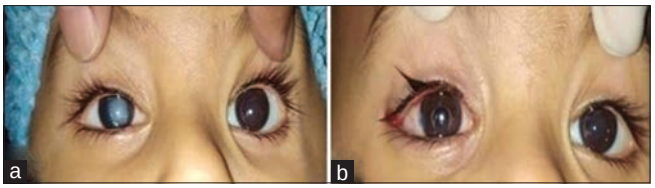


Figure 1: (a) Preoperative photo of a 2-year-old male child with right eye total cataract and left eye pseudophakia. (b) Postoperative photo of the same after right eye cataract surgery

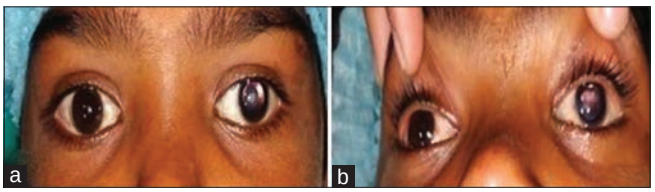


Figure 2: (a) Preoperative photo of a 12-year-old male child with left eye zonular cataract with dense posterior plaque and right eye pseudophakia. (b) Postoperative photo of the same after left eye cataract surgery



Figure 3: (a) Preoperative photo of a 13-year-old male child with right eye membranous cataract and left eye pseudophakia. (b) Postoperative photo of the same after right eye cataract surgery

predictive factor for poor postoperative visual acuity.[23] Children with congenital cataracts should ideally be operated on before the development of these factors, which occur in many cases after 10 weeks of age.[23]

Visual outcome was better in developmental cataract group than congenital cataract group. Severe visual deprivation was suspected to be the cause of poor changes in the postoperative BCVA in congenital cataract group while associated eye comorbidities affected the visual outcome in few cases.

An area of our concern was that after surgery, <20% of patients came for follow-up and visual rehabilitation. A similar situation had been reported in other developing countries where many patients are lost from follow-up after surgery.[24] Reasons for withdrawal include long distance between home and hospital, financial difficulties, poor road infrastructure, ignorance, and lack of awareness to the necessity of long-term follow-up care.

Treatment should not be delayed in pediatric cataract as visual recovery is known to be significantly limited without early intervention. It may be stated that etiology and age at surgery

are equally important factors in prognosis for outcome with primary IOL for the treatment of pediatric cataracts.

CONCLUSION

The current study suggests that primary IOL implantation along with anterior vitrectomy with posterior capsulorhexis is extremely important for pediatric cataract patients. Unilateral cataract has a higher risk of amblyopia. Results come out to be more predictable if early identification, timely referral, and appropriate management protocol are followed. Awareness regarding long-term visual rehabilitation is a must for achieving optimal outcome in such cases.

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.

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Conflicts of interest

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Original Article

Effect of position on the safety and efficacy of neodymium-doped: Yttrium aluminium garnet laser peripheral iridotomy in patients with primary angle-closure disease

ABSTRACT

Purpose: The aim is to evaluate the safety and efficacy of neodymium-doped: yttrium–aluminum–garnet laser peripheral iridotomy (LPI) in the superior versus inferior quadrant in the treatment of primary angle-closure (PAC) disease. **Design:** Randomized, prospective, single-masked, comparative clinical study. **Materials and Methods:** Patients with PAC or PAC suspects were recruited and randomized to receive LPI in the superior or inferior quadrant in both eyes. Patients were masked to the location of treatment in each eye. The main outcome measures assessed were patency of iridotomy, laser parameters, complications, and visual symptoms between the two groups at 1 week and 1 month after the laser intervention. **Results:** A total of 100 patients were recruited, 50 into each group. The mean age was 51.46 ± 7.91 years. Average intraocular pressure (IOP) measurements before LPI was 18.24 ± 5.37 mm Hg and 18.6 ± 5.63 mm Hg in superior LPI and inferior LPI eyes, respectively. After LPI, average IOP was 17.4 ± 3.31 mm Hg and 17.1 ± 3.13 mmHg in superior LPI and inferior LPI eyes, respectively. Inferior LPIs required less use of mean total laser energy ($P = 0.001$) and less number of laser shots ($P = 0.016$) to perforate the iris tissue. There was a lower incidence of iris bleeding and focal corneal damage at the time of treatment; a lower postlaser iritis and lower need for PI enlargement in the inferior LPI group. All the iridotomies were patent at 1 month follow-up. There was no statistically significant difference between the two groups in terms of the dysphotopsias and visual symptoms experienced after the LPI ($P = 0.122$). **Conclusions:** LPI in the inferior quadrant appears to be a safe and efficient alternative to superior LPI with fewer complications in the treatment of PAC disease. Dysphotopsias and visual symptoms following inferior LPI are similar to superior LPI.

Keywords: Dysphotopsias, laser peripheral iridotomy, neodymium: yttrium–aluminum–garnet laser, primary angle-closure suspect, primary angle closure

INTRODUCTION

Laser peripheral iridotomy (LPI) with neodymium-yttrium-garnet laser is considered a standard treatment in patients with primary angle-closure (PAC) disease. It is performed in patients with narrow occludable angles to relieve the pupillary block by balancing the pressure between the anterior and posterior chambers. This can reduce the risk of acute and chronic angle-closure glaucoma. It has largely replaced surgical iridectomy as a simple, noninvasive outpatient procedure without the risks and complications of invasive surgery.[1-3] The complications associated with LPI include transient blurred vision, hyphema, anterior uveitis, the transient rise of intraocular pressure (IOP). Severe and sight-threatening complications such as corneal

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decompensation, cataract, and retinal detachment, although rare, have been reported after LPI.[4-8]

Conventionally, LPI is performed in the superior quadrant so that it is covered by the upper eyelid. Several studies have found superior LPI to be associated with dysphotopsias and visual symptoms in 2.7%–4% of patients.[9-12] Inferior quadrant LPI is used widely in patients with silicon oil tamponade to prevent pupillary block.[13] There are few studies in the literature which have compared the safety and efficacy of LPI performed in the superior and inferior quadrants in patients with PAC glaucoma. A recent study by Ahmadi *et al*. and associates have found inferior LPI to be an efficient method of preventing pupil block with fewer complications.[14]

The purpose of our study was to evaluate the safety and efficacy of neodymium: yttrium–aluminum–garnet (Nd: YAG) LPI performed in the superior versus inferior quadrant in the treatment of PAC disease in phakic patients. The main outcome measures assessed were patency of iridotomy, laser parameters, complications, and visual disturbances postiridotomy between the two groups.

MATERIALS AND METHODS

This prospective, randomized, single-masked study was performed with the approval of the Institutional Ethical Committee. All PAC patients and PAC suspects (PACS) seen during the study period between June 2017 and December 2018 were invited to participate in the study. The inclusion criteria were patients older than 18 years with PACS/PAC posted for LPI who were willing to participate in the study, follow the study protocol and attend the required study follow-up visits. We excluded eyes with PAC glaucoma since we noted a gross difference in terms of best-corrected visual acuity (BCVA) and IOP from the eyes with PACS and PAC. Patients were excluded if they had any previous intraocular surgery, any active intraocular inflammation, or a history of acute angle-closure glaucoma. Before the laser procedure, age, gender, corrected distance visual acuity were recorded. All the patients underwent a comprehensive ophthalmic evaluation, including corrected distance visual acuity, slit-lamp examination, Goldmann applanation tonometry, gonioscopy, and undilated fundus examination. Patients with PAC who had high IOP were started on topical antiglaucoma medications and posted for LPI after normalization of IOP.

Patients were randomized to receive LPI in the superior or inferior location in both eyes by simple randomization. Patients were masked to the location of the LPI performed in each eye. The LPI was performed using the neodymium-yttrium-garnet laser using an Abraham iridotomy lens (Ocular Instruments Inc., Bellevue, Washington, USA). All patients received Pilocarpine 2% eye drops (three applications 10 min apart) 1 h before the procedure and Brimonidine 0.2% eye drops (single application) half an hour before the procedure. The superior LPIs were performed in the supero-temporal quadrant with an attempt to place it as peripheral as possible and under the upper eyelid. Inferior LPI was performed in the inferotemporal quadrant between 6 and 8 o' clock position (for right eyes) and 4 and 6 o' clock positions (for left eyes). The laser spots were applied at the base of iris crypts while avoiding the iris vessels. LPI in both eyes were performed sequentially in the same visit. Intraoperative data collected included laser energy, number of laser shots, and occurrence of any complications. The patients received a single application of Brimonidine 0.2% eye drops after the LPI and IOP was recorded 1 h after the procedure. All patients were put on topical steroid eye drops qid for 1 week.

Patients were followed up after 1 week and 1 month after the laser procedure. At each visit, the BCVA, IOP, gonioscopy, slit-lamp examination and fundus evaluation was performed. The location, size, and patency of the LPI, its distance from the limbus, presence of hyphaema, iritis, corneal damage, cataract was noted. Patients were enquired about the onset of new linear dysphotopsias, glare, haloes or any other visual disturbances at each follow-up visit.

One eye of each patient was included for statistical analysis. In patients with bilateral disease, the right eye was included for analysis.

Statistical analyses were performed using the Statistical Package for the Social Sciences version 15 (IBM, Chicago, Illinois, USA). Paired *t*-tests were used to compare the laser parameters. The Chi-square test was used for all other analyses. Significance was set at $P < 0.05$.

RESULTS

A total of 114 patients were eligible for recruitment into the study, among whom 109 patients underwent the intervention. Our study protocol mandated that each patient received the LPI in either the superior or inferior quadrant in both eyes. Patients in whom this could not be followed were excluded. We included 100 patients who underwent the correct treatment in both eyes and completed their 1-month follow up. Nine patients could not receive LPI in the same quadrant as the randomization protocol and hence were excluded. The baseline demographic and clinical characteristics of these patients are listed in Table 1.

Of the 100 patients, 78 patients had PACS and 22 patients had PAC [Table 1]. The IOP before LPI was 18.24 ± 5.37 mmHg in the superior group and 18.6 ± 5.63 mmHg in the Inferior LPI group. After the LPI, the IOP was 17.4 ± 3.31 mmHg in the superior group and 17.1 ± 3.13 mmHg in the inferior group. The difference in the IOP was not statistically significant.

There was no statistically significant difference in the mean laser energy per shot used (superior: 3.29 ± 0.23 mJ vs. inferior: 3.31 ± 0.16 mJ; $P = 0.6149$). However, there was a statistically significant difference between the two groups in the total energy (superior: 36.78 ± 10.5 mJ vs. inferior: 21.13 ± 7.32 mJ; $P = 0.001$) and the number of laser shots (superior: 10.55 ± 8.64 vs. inferior: 6.45 ± 2.25; $P = 0.0016$) required to perforate the iris.

There was no significant difference between the two groups in the presence of iris bleeding ($P = 0.629$), focal corneal damage ($P = 0.307$), or postlaser iritis ($P = 0.249$), although these complications were slightly higher in the superior LPI group [Table 2]. Eight patients in the superior group and 2 patients in the inferior group required retreatment for enlargement of the LPI, which was done at the 1st week follow-up. This difference was statistically significant ($P = 0.0453$).

All the LPI were patent at the end of 1 month.

In both, the groups, dysphotopsias and glare were the visual disturbances reported following the LPI. Dysphotopsias were reported by three patients in the superior LPI group. The LPI was completely covered by the eyelid in one patient and partially covered in two patients among these two patients in the superior LPI group. Seven patients in the inferior LPI group had visual symptoms in the form of seeing fine lines (three patients) and glare (four patients). The LPI was completely uncovered in six patients and partly covered in 1 among the seven patients reporting visual disturbances in the inferior LPI group. However, there was no statistically

Table 1: Baseline clinical characteristics of the study patients

Characteristics	Superior LPI group	Inferior LPI group	Total
Gender			
Male	14	18	32
Female	36	32	68
Total	50	50	100
Age (years)			
30-39	1	1	2
40-49	11	9	20
50-59	22	17	39
60-69	12	27	29
70-79	4	6	10
Total	50	50	100
BCVA			
<6/60	3	2	5
6/18-6/36	12	10	22
>6/12	35	38	73
Total	50	50	100
Type of PACD			
PACS	39	39	78
PAC	11	11	22
Total	50	50	100
Visually significant cataract			
Present	14	12	26
Absent	36	38	74
Total	50	50	100
IOP mm Hg±SD	18.24±5.37	18.6±5.63	
Antiglaucoma medication usage			
Nil	39	39	78
One	8	11	19
Two	3	0	3
Total	50	50	100

LPI – Laser peripheral iridotomy, BCVA – Best corrected visual acuity, PAC – Primary angle-closure, PACD – PAC disease, PACS – PAC suspect, IOP – Intraocular pressure, SD – Standard deviation

Table 2: Laser parameters and postlaser complications

	Superior LPI	Inferior LPI	*P* (<0.05)
Laser energy			
Mean energy per shot (mJ)±SD	3.29±0.23	3.31±0.16	0.6149
Number of shots (*n*)±SD	10.55±8.64	6.45±2.25	0.0016
Total energy (mJ)±SD	36.78±10.5	21.13±7.32	0.001
Complications			
Iris bleeding	10	12	0.629
Focal corneal damage during LPI	3	1	0.307
Postlaser iritis	9	5	0.249
Postlaser IOP spike	2	1	0.558
Enlargement of LPI/repeat LPI	8	2	0.045
Postlaser visual disturbances			
Present	3	7	0.122
Absent	47	43	
Total	50	50	

LPI – Laser peripheral iridotomy, IOP – Intraocular pressure, SD – Standard deviation

significant difference between the two groups in terms of the visual symptoms experienced after the LPI ($P = 0.122$). Since the number of patients reporting visual disturbances were few, a significant difference was not established between the two groups in terms of the number of laser shots or total energy used.

DISCUSSION

Pupillary block is a significant mechanism causing angle-closure glaucoma. Nd: YAG laser iridotomy to relieve the pupillary block is safe and effective in treating or preventing angle-closure glaucoma.[15-17]

Although LPI is routinely performed in the superior quadrant (superotemporal or superonasal quadrant) there may arise certain situations where we may need to perform it in the inferior quadrant such as significant corneal opacities, absence of crypts in the superior quadrant, inability to perforate iris in the superior quadrant and silicone oil tamponade in retinal surgeries. LPI in the inferotemporal quadrant offers several advantages like ease of access to the LPI site and availability of the superior quadrant in case of significant hyphema (occurring during the LPI) obscuring the inferior iris.

In our study, we found that inferior LPI was easy to perform, required less number of shots and lesser total energy to perforate the iris compared to the superior LPI. The rate of intraoperative and postoperative complications was also less in the inferior LPI group. These findings correlate with the study by Ahmadi *et al*., who have also found inferior LPI to be an efficient technique. Lower laser energy utilized during LPI reduces the incidence of corneal endothelial damage, postoperative rise of IOP, and postlaser iritis.

Many studies have reported the occurrence of dysphotopsias and other visual symptoms like glare, haloes, blurry vision following superior LPI, which can be a cause significant disability and concern.[9-11,14,18] In a recent study by Vanessa and associates,[18] 10.7% of patients with superior LPI demonstrated new linear dysphotopsias and were 3.6 times more likely to develop visual symptoms. Surprisingly, new linear dysphotopsias were four times more common in superior LPI that were partially or completely covered by the eyelid. This is in contrast to the previous knowledge that superior placement of LPI, ensuring complete lid coverage, can avoid dysphotopsias. In our study, there was no difference in the occurrence of visual symptoms in between the two groups.

The limitations of this study were small sample size, lack of long-term follow-up and the fact that we did not elicit a history of visual symptoms before performing LPI which could have helped us in detecting new-onset dysphotopsias after LPI.

CONCLUSIONS

The results of this study may suggest that inferior LPI is a safe and efficient alternative to superior LPI. The low incidence of postoperative dysphotopsias and visual symptoms is an additional advantage. It may be ideal to customize the position of LPI to the individual patient based on ethnicities and eyelid position. A study with a larger sample size and longer follow-up is required to confirm the findings of this study.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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Original Article

Ocular biometric parameters of children with refractive errors in the age group of 6–15 years

ABSTRACT

Background: Refractive errors are one of the leading causes of visual impairment in children. Studies on the association between refractive errors and ocular biometrics have shown inconclusive results; hence, this study aims to examine this relationship. **Objectives:** The objective of this study is to investigate the association between ocular biometrics such as axial length (AL), anterior chamber depth (ACD), lens thickness, vitreous chamber depth (VCD), and corneal curvature (CC) with different refractive errors in children aged 6–15 years. **Materials and Methods:** This was a cross-sectional study and studied 130 eyes of children. Children with congenital and acquired anterior or posterior segment diseases were excluded. All underwent detailed ocular examination, visual acuity measurement, and cyclopegic refraction. Children were divided into emmetropia, myopia, and hypermetropia. Ocular biometrics measured using A-scan and automated keratometer. **Results:** AL, ACD, and VCD significantly increased in the higher levels of myopia ($P \leq 0.0001$), ($P = 0.04$), and ($P \leq 0.0001$), respectively, whereas hypermetropes had the lowest. Spherical equivalence was significantly correlated with AL in myopes ($\rho = -0.624$; $P < 0.0001$) and hypermetropes ($\rho = -0.803$; $P < 0.001$). It was also significantly correlated with ACD more strongly for hypermetropes ($\rho = -0.58$; $P = 0.002$) and VCD more strongly for myopes ($\rho = -0.59$; $P < 0.0001$). There was a significant difference between the age group of 6–10 years and 11–15 years for AL ($P = 0.001$), ACD ($P \leq 0.0001$), VCD ($P = 0.001$), and CC ($P = 0.03$). **Conclusion:** AL and VCD make the greatest contribution to refractive errors. ACD has more important role in hypermetropes and VCD in myopes. A relative higher AL, ACD, VCD, and CC were found in the age group of 11–15 years.

Keywords: Anterior chamber depth, axial length, corneal curvature, lens thickness, refractive errors, spherical equivalence, vitreous chamber depth

INTRODUCTION

Ocular biometrics such as axial length (AL), anterior chamber depth (ACD), vitreous chamber depth (VCD), lens thickness (LT), and corneal curvature (CC) are among the most important factors affecting in refractive errors, and emmetropization is a result of a balance among these biometric components.[1] The studies on the relationship between refractive errors and ocular biometrics have shown inconclusive results, and no such study has been conducted in children from South India. Therefore, this study aims to examine the relationship between the various ocular biometric parameters such as AL, ACD, VCD, LT, and CC with different refractive errors in the age group of 6–15 years.

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MATERIALS AND METHODS

- Study design: Cross-sectional study
- Study setting: Department of ophthalmology of a tertiary care center in Central Kerala
- Study participants: Children of the age group of 6–15 years attending the ophthalmology outpatient

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department (OPD), for their eye check-up during a period of 1 year from May 2018 to April 2019
- Study period: 1 year
- Sample size: 130 eyes.

Sampling technique

The sample size was determined and calculated using the following formula (according to Bueno-Gimeno *et al.*[2]):

$$\frac{4SD^2}{d^2}$$

Where, SD = standard deviation of the variable (AL), d = precision of study = 0.02 mm.

A total of 130 eyes of 71 children who came for their eye check-up were evaluated after obtaining consent from parent/guardian.

Inclusion criteria

Children attending the ophthalmology OPD for their eye check-up in the age group of 6–15 years were included in the study.

Exclusion criteria

- Children with congenital anterior or posterior segment disease
- Children with acquired anterior or posterior segment disease
- Children with a history of ocular surgery, trauma, or on any long-term ocular medication were excluded from the study.

Methodology

After obtaining the ethical clearance from the institutional research board, we started the data collection. Informed consent from the parents or guardians of the children fulfilling the inclusion criteria was obtained, and a detailed history was taken. It included the chief complaints, previous ocular and medical history. All children then underwent a detailed ocular examination, and any anterior or posterior segment diseases were ruled out. Anterior segment was first assessed by a torch light and then followed by a slit-lamp examination. Visual acuity measurement was done by a Snellen's chart (or E chart or picture chart). It was followed by a cyclopegic refraction test after instilling Homatropine 2% eye drop (1 drop every 10 min for three times). After 1 h, pupils were fully dilated. The child was then subjected to retinoscopy and autorefraction. Following this, a detailed dilated fundus examination was also performed using a direct ophthalmoscope.

After 1 week, the participants were again reviewed for a post mydriatic test and ocular biometry. Children underwent subjective refraction, and then, the type of refractive error along with the spherical equivalent (SE) was calculated (SE = sphere + cylinder/2). The sample was divided into three main groups of emmetropic eyes (as control), myopic eyes and hypermetropic eyes. Emmetropia was defined as the presence of a SE between +0.75D and −0.25 D.[2] The myopic group was further divided into low (SE of −0.5D to −3D), moderate (SE of −3.25 D to −6D), and high (SE of more than − 6D). The hypermetropic group was similarly divided into three subgroups as low (SE of +1D to +3D), moderate (SE of +3.25D to +6D), and high (SE of more than +6D); (however moderate and high hypermetropic samples were not obtained in this study). In order to assess the relationship between age and ocular biometry, the participants were subgrouped into 6–10 years and 11–15 years also.

Measurement of ocular biometrics was performed after the above-mentioned tests and procedures. For AL, ACD, LT, and VCD measurement, an A-scan ultrasound (Sonomed 300-A) was used (even though immersion, indentation technique was accepted for this study). After instilling 1 drop of local anesthethic, proparacaine drop in the eye, readings were taken with the child seated. The onscreen settings were set to phakic and while measuring, the probe was perpendicular to the cornea and did not indent it. The AL, ACD, and LT were displayed in the monitor, whereas VCD was calculated by subtracting the total of ACD and LT from the AL. The CC was measured using an automated keratometer (Canon RK-5). Finally, the total number of eyes studied was correlated with their ocular biometry.

Statistical analysis

Statistical analysis was performed using the SPSS version 21.0 software (SPSS software Trial version from IBM). The mean and standard deviation were calculated in different levels of refractive errors, and the ocular biometric parameters were assessed using one-way ANOVA test and Bonferroni *post hoc* test. Correlations were examined using Spearman's rho. Mann–Whitney U-test was used to assess the ocular biometric components between the two age groups. $P < 0.05$ was considered statistically significant in all statistical tests.

RESULTS

In total of 130 eyes of 71 children, 42% of the total sample was myopic [Figure 1].

The mean age of the whole sample was 8.7 years (range, 6–15 years). The mean of spherical equivalence (SE) was −1.06±(3.04) D (range, −11.5D–D) [Figure 2].

The mean AL, ACD, VCD, LT, and CC of the whole sample were 22.75± (1.35) mm, 3.38± (0.33) mm, 15.76± (1.25) mm, 3.59± (0.26) mm, and 43.94± (1.17) D, respectively.

Table 1 summarizes the mean ocular biometric measurements such as AL, ACD, LT, VCD, and CC at different levels of refractive error [Table 1]. AL, ACD, and VCD significantly increased at higher levels of myopia ($P \leq 0.0001$), ($P = 0.04$), and ($P \leq 0.0001$), respectively, and hypermetropes had the lowest. LT was the highest for hypermetropes (3.66 ± 0.36) mm and high myopes (3.79 ± 0.28) mm.

One-way ANOVA showed significant differences of the mean between the three main groups (emmetropia, myopia, and hypermetropia) for AL ($P < 0.0001$), ACD ($P = 0.03$), and VCD (p=<0.0001), but not for LT and CC [Table 2].

Correlations by refractive state-spearmans correlation:

1. AL and CC - Significant correlation was found between AL and CC ($\rho = -0.174$, $P = 0.04$) and strongly correlated in the emmetropic group ($P \leq 0.0001$) [Table 3 and Figure 3]
2. AL and LT - No correlation was found between AL and LT ($\rho = -0.02$; $P = 0.80$) [Table 4 and Figure 4]
3. SE and AL - SE was significantly correlated with AL in myopes ($\rho = -0.62$, *P.* 0.0001) and hypermetropes ($\rho = -0.80$: P <0.0001) [Figure 5]
4. SE and ACD - Statistically significant differences were found between SE and ACD ($\rho = -0.179$; $P = 0.04$). SE was more strongly correlated with ACD in hypermetropes ($P = 0.002$) than myopes ($P = 0.01$) [Table 5 and Figure 6]
5. SE and VCD - Significant correlation between SE and VCD was noted ($\rho = -0.628$; $P \leq 0.0001$). SE was more strongly correlated with VCD in myopes (P y 0.0001). However, this study could not find any correlation between degree of myopia and change in VCD [Table 6 and Figure 7]. When we calculated ACD/VCD ratio, as the degree of myopia increases, the ACD/VCD ratio decreases [Table 7]
6. No significant differences were found between SE and LT ($\rho = -0.109$; $P = 0.21$) [Figure 8], nor between SE and CC ($\rho = -0.127$ $P = 0.14$) [Figure 9].

When we divided the children into two groups 6 to10 years and 11–15 years, the mean and standard deviation values of

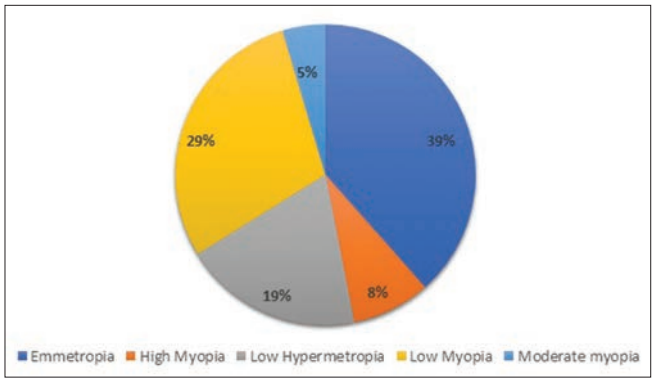


Figure 1: Types of refractive errors and its percentage

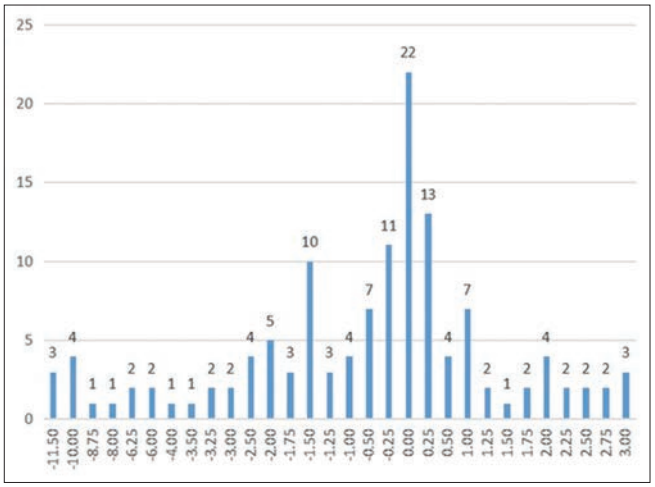


Figure 2: Frequency distribution of spherical equivalence of the whole sample

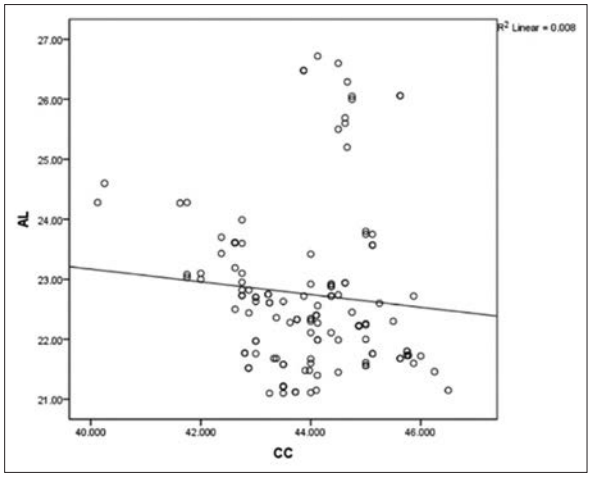


Figure 3: Scatter graph of axial length and corneal curvature

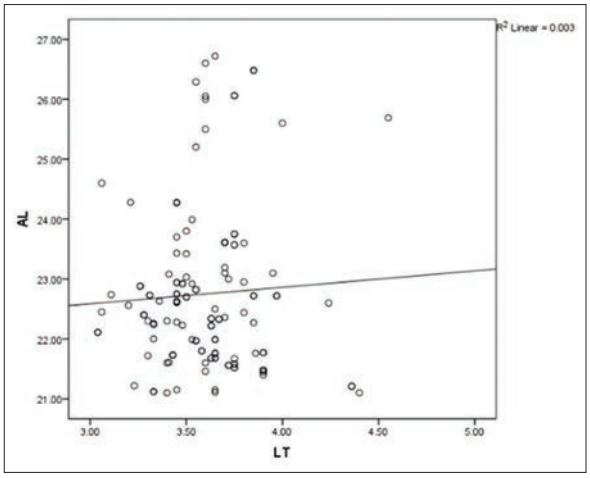


Figure 4: Scatter graph of axial length and lens thickness

Table 1: Mean and standard deviation of spherical equivalence, axial length, anterior chamber depth, lens thickness, vitreous chamber depth and corneal curvature in different levels of refractive errors

	n	SE (D)	AL (mm)	ACD (mm)	LT (mm)	VCD (mm)	CC (D)
Emmetropia	50	0.50±0.22	22.44±0.68	3.41±0.24	3.53±0.20	15.47±0.66	43.78±1.12
Low myopia	38	−1.51±0.69	22.72±0.82	3.36±0.28	3.59±0.24	15.77±0.81	43.80±1.48
Moderate myopia	6	−4.33±1.31	23.74±1.38	3.48±0.12	3.48±0.09	16.79±1.36	44.77±0.51
High myopia	11	−9.43±1.92	26.18±0.36	3.60±0.32	3.79±0.28	18.77±0.83	44.63±0.58
Low hyperopia	25	1.86±0.72	21.64±0.57	3.23±0.50	3.66±0.36	14.75±0.50	43.98±0.90

n – Total number, SE – Spherical equivalence, AL – Axial length, ACD – Anterior chamber depth, LT – Lens thickness, CC – Corneal curvature, VCD – Vitreous chamber depth

Table 2: Significance values for each biometric component between emmetropia, myopia, and hypermetropia by one-way ANOVA

	F	*P*
AL	26.21	<0.0001*
ACD	3.48	0.03*
VCD	25.43	<0.0001*
LT	2.33	0.10
CC	0.80	0.45

*Signifies $P<0.05$ which is statistically significant. AL – Axial length, ACD – Anterior chamber depth, LT – Lens thickness, CC – Corneal curvature, VCD – Vitreous chamber depth

Table 3: Correlation between axial length and corneal curvature

	Correlation coefficient (ρ)	*P*
Emmetropia	−0.67	<0.0001*
Myopia	−0.02	0.87
Low myopia	−0.24	0.13
Moderate myopia	−0.52	0.28
High myopia	−0.52	0.09
Hypermetropia	0.08	0.68

*Signifies $P<0.05$ which is statistically significant

Table 4: Correlation between axial length and lens thickness

	Correlation coefficient (ρ)	*P*
Emmetropia	−0.14	0.31
Myopia	0.18	0.19
Low myopia	−0.068	0.68
Moderate myopia	0.98	<0.0001*
High myopia	−0.32	0.33
Hypermetropia	−0.29	0.25

*Signifies $P<0.05$ which is statistically significant

ocular biometric parameters by age are shown in [Table 8]. Mann–Whitney test revealed significant difference between the two age groups for AL ($P = 0.001$), ACD ($P \leq 0.0001$), VCD ($P = 0.001$), and CC ($P = 0.03$), but not for LT ($P = 0.06$).

DISCUSSION

The refractive error of the eye is governed by the multifactorial condition which involves AL, corneal and lens power, ACD, and VCD of the eye, due to its variations of these biometric components during the growth of the eye.[3] It has been demonstrated that for the progression of myopia, an increase in the AL of the eyeball is the principal morphological factor related to it in children,[4-6] and similarly, shorter AL is the main morphological factor which is related to hypermetropia.[7] Furthermore, in certain studies, part of refractive errors has also been attributed to ocular biometrics such as ACD, LT, VCD, and CC.[8,9]

In this study, we described the relationship between refractive status and biometric components in different types and levels of refractive errors in children between the age group of 6–15 years. Forty-two percent of the total sample was myopic which agrees with the information that myopia is the most prevalent refractive error worldwide. The mean age of the whole sample was 8.7 years (range, 6–15 years). The mean of SE was −1.06± (3.04) D (range, −11.5D–3D). The mean AL, ACD, VCD, LT, and CC of the whole sample were 22.75 (1.35) mm, 3.38± (0.33) mm, 15.76± (1.25) mm, 3.59± (0.26) mm, and 43.94± (1.17) D, respectively.

Significant differences between the three main groups, i.e., myopia, emmetropia, and hypermetropia were found for AL ($P < 0.0001$), ACD ($P = 0.03$), and VCD ($P \leq 0.0001$). Among the different components, AL, ACD, and VCD made the most contribution to changes in refractive errors whilst LT ($P = 0.10$) and CC ($P = 0.45$) showed less variation, similar to study made by Hashemi *et al.*[10] In most of the previous studies, AL and VCD were the most important components in relation to refractive errors,[11,12] which is similar to our results.

Previous reports such as Warrier *et al.*[8] and Mallen *et al.*[13] also discussed about having a longer AL and its components such as VCD and ACD in myopes and reverse in hyperopes which is in accordance with our results. AL, ACD, and VCD significantly increased at higher levels of myopia ($P \leq 0.0001$), ($P = 0.04$), ($P \leq 0.0001$), respectively, in our study and hypermetropes had the least values.

One of the findings in our study is a higher LT in hyperopes which can be explained by a hyperope accommodating more to focus an image which causes lens to thicken and subsequently leading to a lesser ACD.

Table 5: Correlation between spherical equivalence and anterior chamber depth

	Correlation coefficient (ρ)	*P*
Emmetropia	0.24	0.08
Myopia	−0.31	0.01*
Low myopia	−0.23	0.15
Moderate myopia	0.38	0.44
High myopia	0.27	0.40
Hypermetropia	−0.58	0.002*

*Signifies $P<0.05$ which is statistically significant

Table 6: Correlation between spherical equivalence and vitreous chamber depth

	Correlation coefficient (ρ)	*P*
Emmetropia	−0.19	0.17
Myopia	−0.59	<0.0001*
Low myopia	−0.06	0.68
Moderate myopia	−0.97	0.001*
High myopia	−0.02	0.94
Hypermetropia	−0.31	0.12

*Signifies $P<0.05$ which is statistically significant

Table 7: Anterior chamber depth/vitreous chamber depth ratio in different levels of refractive error

	ACD/VCD
Emmetropia	0.22
Low myopia	0.21
Moderate myopia	0.20
High myopia	0.19
Hypermetropia	0.21

ACD – Anterior chamber depth, VCD – Vitreous chamber depth

Table 8: Mean and standard deviation values of ocular biometric components between 6-10 years and 11-15 years age group

	Mean±SD	
	6-10 years (*n*=105)	11-15 years (*n*=25)
SE (D)	−0.95±2.91	−1.53±3.57
AL (mm)	22.60±1.34	23.37±1.23
ACD (mm)	3.32±0.31	3.63±0.32
VCD (mm)	15.66±1.29	16.20±1.00
LT (mm)	3.61±0.24	3.52±0.30
CC (D)	44.05±1.20	43.51±0.97

AL – Axial length, ACD – Anterior chamber depth, LT – Lens thickness, CC – Corneal curvature, VCD – Vitreous chamber depth, SD – Standard deviation, SE – Spherical equivalence

In our study, SE was having a correlation with AL in myopes ($P \leq 0.0001$) and in hypermetropes ($P \leq 0.0001$) which is in accordance with previous reports.[4-7] SE showed a strong correlation with VCD in myopes ($P \leq 0.0001$) which is in agreement to previous study,[14] which states VCD is the main reason for the changes in refraction in case of myopia. When we took ACD/VDC ratio, as the degree of myopia increases, the ratio decreases, which signifies that VCD disproportionately increased at higher levels of myopia also. Zhu *et al*.[15] state that genetic changes responsible for myopia mostly cause changes in the posterior segment. However, SE had a more important correlation with ACD in hyperopes ($P = 0.002$), which is to be highlighted as only a few studies have investigated this relationship between anterior segment parameters and hyperopia.[10]

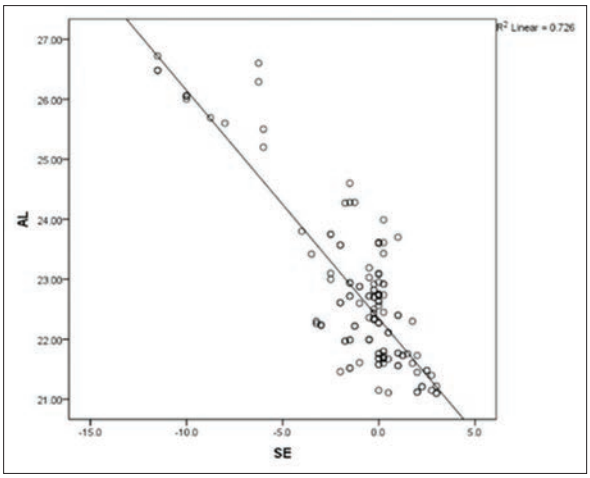


Figure 5: Scatter graph of spherical equivalence and axial length

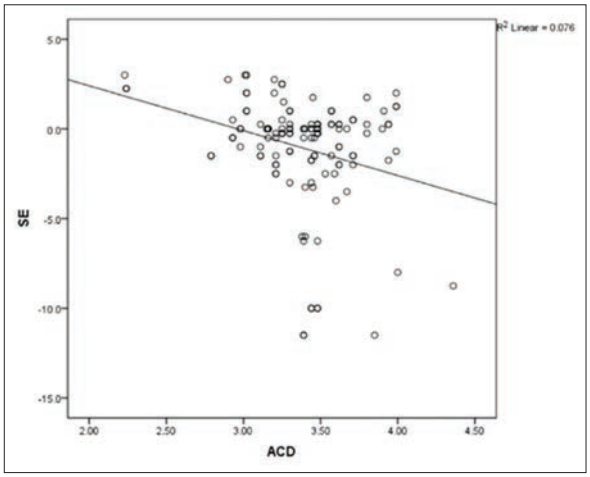


Figure 6: Scatter graph of spherical equivalence and anterior chamber depth

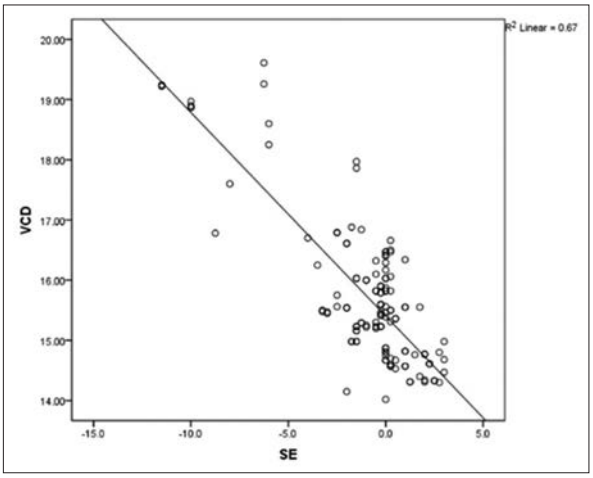


Figure 7: Scatter graph of spherical equivalence and vitreous chamber depth

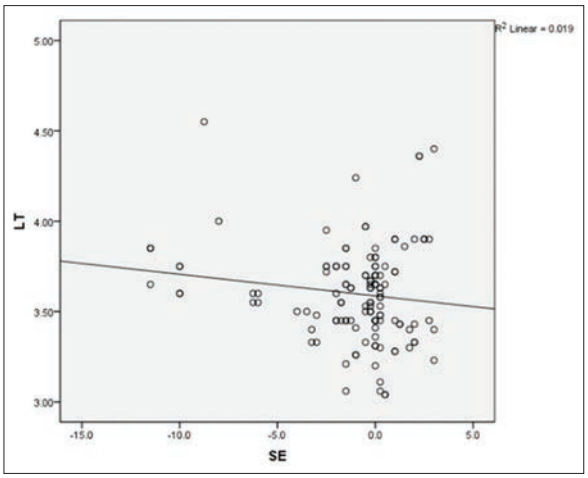


Figure 8: Scatter graph of spherical equivalence and lens thickness

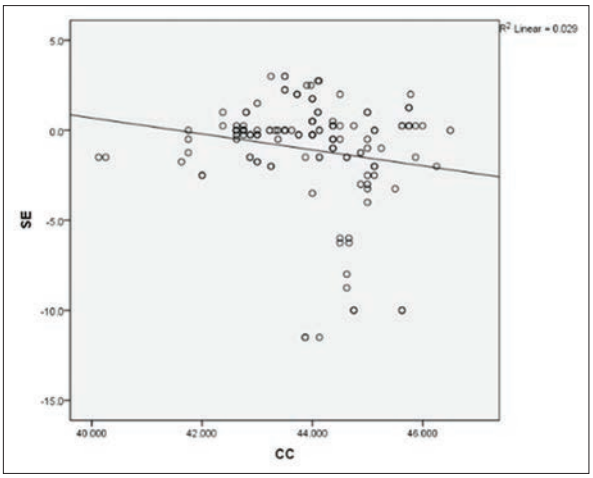


Figure 9: Scatter graph of spherical equivalence and corneal curvature

Hashemi *et al*.[10] conducted a cross-sectional, population-based study with large sample size at Iran, to investigate the association between ocular biometrics with different levels of refractive error in age group of 40–64 years. The study revealed that corneal power and AL make the greatest contribution to SE in high hypermetropia and high myopia. Hashemi *et al*. in their study found that corneal power increased at higher levels of myopia and decreased at higher levels of hyperopia; but no such correlation was found in our study between AL and CC. The role of cornea in the appearance and progression of refractive errors has been the subject of study since years. Touzeau *et al*.[16] demonstrated no relationship between refractive errors and CC; although CC has been linked to AL especially in emmetropes. This is in accordance with our study where we obtained similar results ($P \leq 0.0001$). This would be expected if we consider that during emmetropization, an increased AL of eye will be counteracted by an increase in the corneal radius to maintain emmetropia. Paradoxically, other authors have found that the most myopic subjects therefore with large AL have small corneal radi.[17,18] Scott explained this paradox by distinguishing between the normal growth of the eye and abnormal growth that occurs during the development of myopia. In the first case, the cornea becomes flatter as the eye develops and increases in size, whereas in the latter case, the cornea cannot continue to flatten and may even curve because of stretching of the eye.[17] Other authors found no relationship between AL and CC in any levels of myopia.[12,19] Cornea seems to play at preserving emmetropia.

Bhardwaj and Rajeshbhai[20] conducted a study at Jaipur on 480 eyes with subject's ages ranging from 0 to 60 years to find out the role of AL and ACD in refractive status of the eye in different age groups and the study concluded that myopes have a longer AL and hypermetropes tend to have shorter AL when compared to that of emmetropes. When we divided the participants into two groups (6–10 and 11–15 years), a relative higher AL, ACD, VCD, and CC were found in the latter group. However, no difference in mean noted in LT between the two groups. This also supports the process of emmetropisation. Similar findings were observed by Bhardwaj and Rajeshbhai in their study.[20] Zadnik *et al*.[4] found that there is a general pattern of ocular growth between the age group of 6–14 years which is found in our study.

CONCLUSION

In our study, myopia is the most common refractive error. In children aged 6–15 years, AL and VCD make the greatest contribution to refractive errors. Anterior segment biometric components have a more important role in hypermetropes than myopia and VCD is the most affected in myopes especially at higher myopia. The CC and LT are not determining factors for SE. A relative higher AL, ACD, VCD, and CC were found in the age group of 11–15 years, which thus supports the process of emmetropisation and the general pattern of ocular growth between the ages of 6–15 years.

Limitations of the study

The study was conducted in a small sample size; hence, the results are limited to a small population. We have obtained the ocular biometric parameters by a scan ultrasound; however, immersion technique or the optical technique would have given more accurate results. Moderate and high hypermetropia samples were not obtained; hence, its correlation was not assessed.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Relationship among standard vision tests, quality of life, and ability to do daily activities in patients with glaucoma

ABSTRACT

Background and Objectives: (1) To assess the quality of life (QoL) in patients with glaucoma by (a) clinical assessment, (b) subjective (Visual Functioning Questionnaire-25 [VFQ-25]), and (c) objective (Assessment of Disability Related to Vision [ADREV]) tests and (2) to find out the relationship between glaucoma stages and QoL. **Materials and Methods:** This cross-sectional study includes 100 patients attending the glaucoma clinic of a tertiary institution in Kerala. Best-corrected visual acuity, baseline intraocular pressure, slit-lamp and fundus examination, gonioscopy, and visual field examination were carried out. Patients were categorized as early, moderate, and advanced on the basis of disc damage likelihood scale (DDLS) and modified Hodapp–Parrish–Anderson criteria. QoL was assessed subjectively using VFQ-25 and objectively by ADREV test by assessing the ability to perform activities of daily living. Contrast sensitivity and stereopsis were the other parameters assessed. **Results:** Of the 100 patients, 50 (50%) were POAG, 46 (46%) were PACG, and 4 were secondary glaucoma. Based on the DDLS and Anderson criteria, there were 33 early, 34 moderate, and 33 advanced glaucoma cases. The mean ADREV/VFQ scores were as follows: early, 56.9/81.1; moderate, 54.9/75; and advanced, 45.8/52.6. In ADREV tasks, the lowest mean score was for motion detection (5.1) and maximum score was for ambulation (6.1) in the study population. Patients with advanced glaucoma have difficulty in detecting motion (4.1), recognizing street signs (4.3), and color matching (4.8). Stereopsis was seen in 60% of patients with early, 29% of moderate, and 6% of advanced glaucoma. Contrast sensitivity was also reduced with glaucoma progression. **Conclusion:** ADREV (objective) scores correlate significantly with VFQ (subjective) scores in all the three categories of glaucoma. ADREV (objective test) scores correlate better with the severity and stages of glaucoma and degree of impairment patients experience than VFQ-25 (subjective test). With respect to QoL, patients with glaucoma faced difficulty in performing fine tasks. However, even advanced glaucoma cases were able to carry out their daily activities without much help. Stereopsis and contrast sensitivity were the most affected with advancement of disease.

Keywords: Assessment of Disability Related to Vision, contrast sensitivity, disc damage likelihood scale, glaucoma, Hodapp–Parrish–Anderson, quality of life, stereopsis, Visual Functioning Questionnaire-25

INTRODUCTION

Glaucoma is a chronic progressive optic neuropathy characterized by loss of retinal nerve fiber layer, recognized clinically as loss of neuroretinal rim, and visual field defects.[1] For most patients, having sufficient vision to perform their daily activities is a high priority. Understanding this aspect of a disease is provided by tests evaluating quality of life (QoL).

Glaucoma may affect a patient's QoL in several ways such as the psychological effects arising from the fear of blindness leading to anxiety and depression, decreased visual field and ultimately visual acuity, the potential side effects of treatment, and the economic burden due to the cost of visits and therapy and loss of income because of absenteeism from work.

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The clinician performs a battery of tests to assess the structure of the optic disc and its function, correlates them, based on which he/she decides on the stage of severity of glaucoma, and advises treatment to prevent its progression. The ultimate goal of glaucoma management is the preservation of patient's visual function and QoL. This complicated clinical perspective is difficult for the patient to understand.

Indicating to a patient, a functional deficit in an activity of daily living would be expected to have a more powerful impact than commenting on a concern regarding intraocular pressure (IOP) or change in visual field. When patients understand their disease better, they take better care of themselves. The goal of the treatment of patients with glaucoma is to prevent disability or, if disability already exists, to repair the disability or at the least to prevent further disability from developing. Hence, the ultimate goal in the management of glaucoma is maintenance of QoL through preservation of vision. However, very often, this becomes secondary to assessment of IOP, visual field changes, and optic disc appearance.

The National Eye Institute (NEI)–Visual Function Questionnaire (VFQ)-25 describes the patient's satisfaction with his/her visual function and how visual ability impacts his/her life.[2,3] A better understanding of this NEI-VFQ-25 questionnaire can improve the patient–physician interaction.

The various tasks that are affected at various stages of the disease can also be objectively assessed by the Assessment of Disability Related to Vision (ADREV).[4] This performance-based assessment is also validated and easily reproducible.

Although each approach provides a unique and important perspective in understanding the lives of patients with glaucoma, studies that integrate all the three methods are very few and have not been done in India. The purpose of our study is to assess the strength of relationship between clinical, subjective, and objective measures of visual function in glaucoma. Hence, the current study aims to have a broader look on glaucoma and its treatment by assessing the QoL. It also helps plan our treatment strategies wisely, so that patients QoL is given equal importance along with the medical and surgical management.

MATERIALS AND METHODS

A cross-sectional observational study was done on 200 eyes of 100 patients with glaucoma who attended the glaucoma clinic of a tertiary institution in Kerala. The institutional ethics committee and institutional review board approved this study. The first 100 consecutive patients previously diagnosed and undergoing treatment for glaucoma were selected for the study.

Individuals with neurological or musculoskeletal problems that would influence their performance in different tests in the study, any medical condition that would preclude the subject from providing reliable or valid data, incisional eye surgery within the past 3 months, and visual impairment due to other causes were excluded from the study.

Each patient underwent a complete ophthalmic work up including history,best corrected visual acuity,slit lamp examination and a dilated fundus examination using an indirect ophthalmoscope.They also underwent a complete glaucoma workup including Goldmann applanation tonometry,gonioscopy,optic disc and retinal nerve fibre layer evaluation using 90 D lens by slitlamp biomicroscopy.

Patients were categorized on the basis of disc damage likelihood scale (DDLS)[5] and modified Hodapp–Parrish–Anderson (HPA) criteria[6] into three groups:

1. Group 1: Early (early glaucomatous loss (MD < 6DB) with DDLS Stage 1–4 in both eyes)
2. Group 2: Moderate (moderate glaucomatous loss with DDLS Stage 1–4/5–7 in better eye and 5–7/8–10 in worst eye)
3. Group 3: Advanced (advanced glaucomatous loss with DDLS Stage 8–10 in both eyes).

Standard methods of visual function testing including visual acuity, stereopsis using stereo fly test, visual field testing using Humphrey's field analyzer, and contrast sensitivity using Pelli Robson chart were done.

A validated Malayalam translation of the NEI-VFQ-25 was explained to the patients, and their response was recorded. All questions in NEI-VFQ-25, except two (related to parameter "driving"), were included in this study. The total score of VFQ-25 was calculated according to the guidelines in NEI-VFQ-25 scoring algorithm. Patients were also assessed for the performance of daily activities using ADREV.

Tasks included in ADREV are performed by the patient in the following order.

1. Reading in reduced illumination
2. Recognizing facial expression
3. Detecting motion
4. Recognizing street sign
5. Locating objects

6. Ambulating
7. Placing peg into different sized holes
8. Telephoning
9. Matching socks.

The tasks were performed with both eyes viewing and wearing their present habitual refractive correction. Tasks such as reading in reduced illumination, recognizing facial expression, and detecting motion test were carried out in a dark room, and the rest of the tasks were done in ambient lighting. Statistical analysis was performed using SPSS 21.0 version (Statistical Package for the Social Sciences 21.0 version). Pearson's correlation test was used for calculating correlation coefficient. Differences were considered statistically significant when the *P* value was 0.01 or less.

RESULTS

The study population consisted of 100 patients with glaucoma aged between 35 and 75 years who attended the glaucoma clinic.

Based on the DDLS and HPA criteria, the study patients were divided into three groups:

1. Group 1: Early (early glaucomatous loss [MD <6 DB] with DDLS Stage 1–4 in both eyes)
2. Group 2: Moderate (moderate glaucomatous loss with DDLS Stage 1–4/5–7 in better eye and 5–7/8–10 in worst eye)
3. Group 3: Advanced (advanced glaucomatous loss with DDLS Stage 8–10 in both eyes.

The number of patients in each group is shown in Figure 1. Majority of the patients were between 55 and 75 years in the study population. In the individual groups, the mean age of all the patients was comparable [Figure 2]. However, the mean age of patients with early glaucoma was low compared to the moderate and advanced cases. Gender proportion was comparable in the present study. There were about 59 males and 41 females in the study. The number of cases of primary open angle (50) and angle closure (46) was almost equal. There were four secondary glaucoma cases, out of which two were pseudoexfoliative glaucoma, one angle recession glaucoma, and one combined mechanism glaucoma.

Clinical characteristics of the study population

The clinical characteristics of the study population are shown in Table 1. In 100 patients, the mean visual acuity was found to be 0.269. The total VFQ score was in the range of 13.4–94.7. The mean score was found to be 69.6. When considering the ADREV scores, the maximum score obtained was 63 and the minimum was 31. The mean ADREV score was 52.5. The contrast sensitivity also showed a wide range. The maximum value obtained was 2.25, 0.15 being the minimum score. As far as stereopsis is concerned, it was seen in only 32 patients.

Assessment of Disability Related to Vision versus Visual Functioning Questionnaire

The mean ADREV versus VFQ scores [Figure 3] are as follows:

1. Group 1 (early) – 56.9/81.1
2. Group 2 (moderate) – 54.9/75
3. Group 3 (advanced) – 45.8/52.6.

There is a proportionate decrease in both the scores in the study population with respect to the severity of glaucoma.

Stereopsis

Stereopsis was seen to be grossly affected with glaucoma progression. In patients with advanced glaucoma, only two people had gross stereopsis [Figure 4].

Contrast sensitivity

Contrast sensitivity in the entire study population ranges from 0.15 to 2.25. The mean contrast sensitivity of patients with early glaucoma was about 1.22, whereas in advanced glaucoma, the mean has reduced drastically to 0.58. Contrast sensitivity also showed a declining trend with glaucoma progression [Figure 5]. Even in patients with early glaucoma, contrast sensitivity is comparatively low when compared to the normal population. Patients with advanced glaucoma have very low contrast sensitivity, which can adversely affect their QoL.

Assessment of Disability Related to Vision individual tasks

Patients with early glaucoma scored reasonably good for all the tasks except motion detection. Moderate glaucoma cases also had difficulty in detecting motion and recognizing street signs. In advanced glaucoma, tasks such as motion detection, street sign recognition, and matching colors had very low scores. Detecting motion was the task that was difficult for all the three categories of glaucoma. Even the advanced glaucoma cases had a fairly good score for ambulation. Reading and recognizing facial expression and ambulation were the tasks that the patients with advanced glaucoma performed well [Figure 6].

Correlation among the study variables

There was a strong positive correlation of 0.78 ($P < 0.01$) between ADREV (objective) and VFQ scores (subjective) [Table 2]. DDLS showed a higher correlation coefficient for ADREV (objective) ($r = -0.61$, $P < 0.01$) than VFQ ($r = -0.54$, $P < 0.01$). Visual acuity had a higher correlation with ADREV than VFQ scores. Contrast sensitivity score

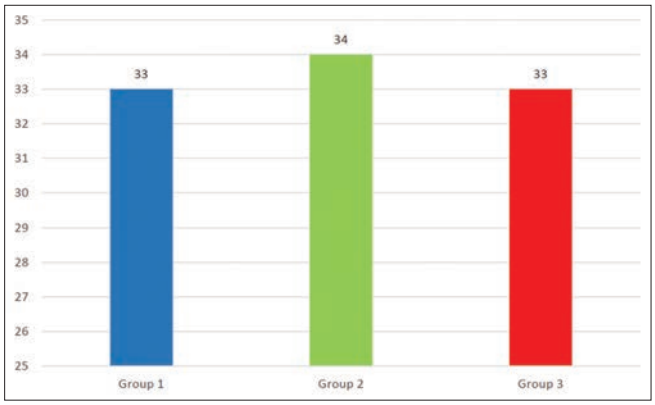


Figure 1: Number of patients in each group

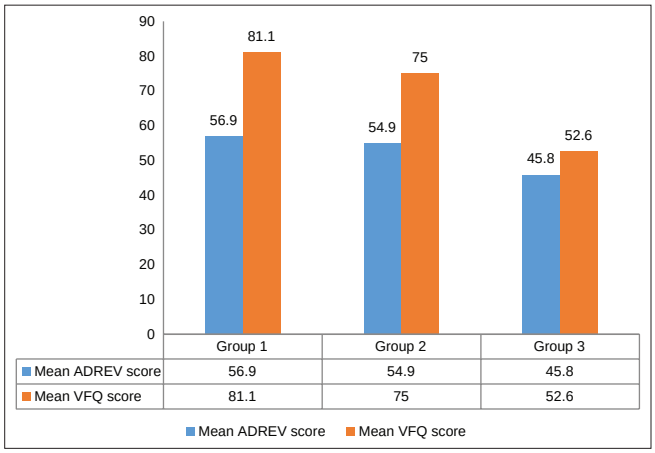


Figure 3: Comparison of subjective and objective scores

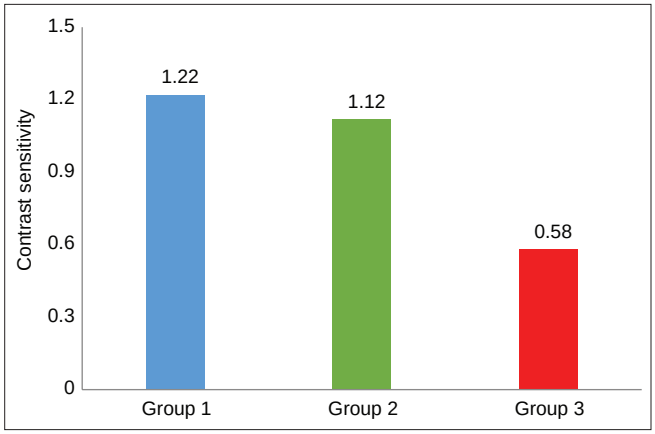


Figure 5: Contrast sensitivity of the study population

showed a moderate correlation with both ADREV ($r = 0.53$, $P < 0.01$) and VFQ ($r = 0.58$, $P < 0.01$).

DISCUSSION

The awareness of the correlation between clinical assessment of visual function and QoL has prompted new approaches to the management of glaucoma. Clinical trials strongly suggest

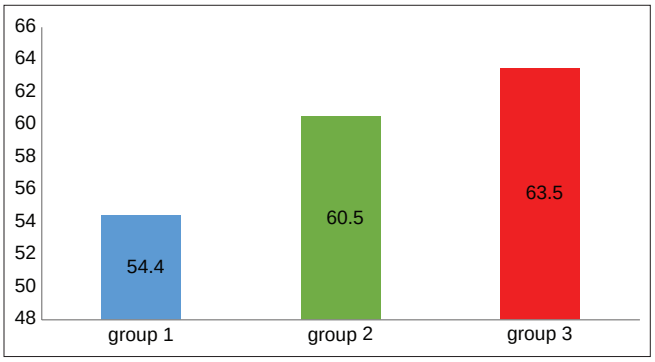


Figure 2: Mean age of individual group

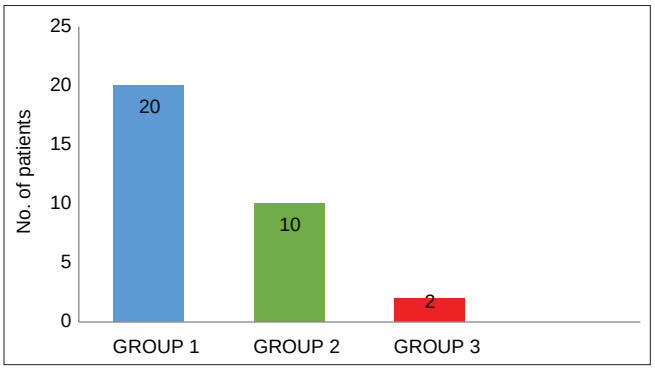


Figure 4: Stereopsis of the study population

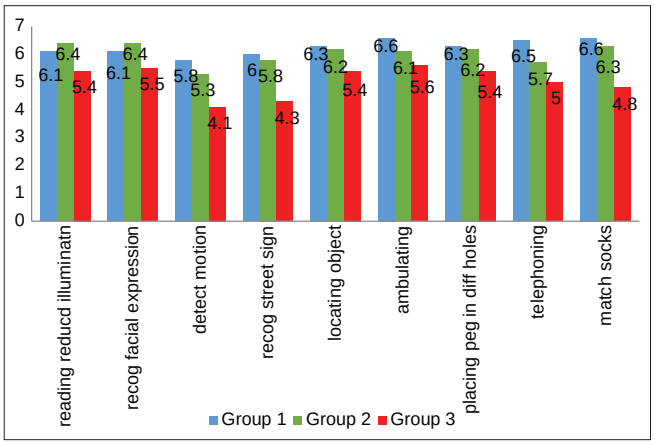


Figure 6: Individual Assessment of Disability Related to Vision scores of various groups

that changes in QoL should be the key outcome measure of treatment.

In the present study, the mean age of the study population varies from 35 to 75 years. Majority were in the age group of between 55 and 75 years. The prevalence of glaucoma increases with advancing age.[7] Our study also showed an increased prevalence with age.

Out of 100 patients, there were 41 females and 59 males. In our study, there was not much significant prevalence

by gender. Women are at higher risks for angle-closure glaucoma, but there is no clear gender predilection for open-angle glaucoma.[8] In our study, also, majority of the angle-closure glaucoma cases were female. In the current study, in addition to the routine clinical assessment, we asked the patients about their QoL and we observed how patients with glaucoma actually function.

Assessment of Disability Related to Vision versus Visual Functioning Questionnaire

There was a statistically significant correlation between the total scores of ADREV and the NEI-VFQ-25 and between domains of the NEI-VFQ-25 and related ADREV tasks as per the study by Lorenzana *et al*.[9] Our study also showed a significant correlation between subjective (NEI-VFQ-25) and objective (ADREV) tests.

Clinical assessment versus Assessment of Disability Related to Vision versus Visual Functioning Questionnaire

The total ADREV score showed a more correlation with various clinical assessment test than the NEI-VFQ. This was similar to a study conducted by Richman *et al*.[10] The total ADREV score provides more accurate representation of disease severity, in terms of functional ability, than the total NEI-VFQ-25 score.

There are several possible explanations for the lack of concordance between the clinical and subjective tests. Self-reports are based on patient's understanding of what the presented task might involve, their assessment of the task's relative difficulty, and their own perceptions of their ability to perform that task. Performance-based testing removes this subjectivity and simply involves observing a patient's actual ability to perform a given task.

There are several discrepancies between self-report and performance-based measures in our study similar to studies by Viswanathan *et al*.,[11] Friedman *et al*.,[12] and Kempen *et al*. Subjects with the same severity of disease clinically had more variation in their responses to QoL questions than the amount of variation in how they performed the tasks of daily living in our study. This is to be expected, because QoL is influenced by a wide variety of components; more involved are ability such as detecting motion.

Assessment of Disability Related to Vision tasks

The tasks are designed in such a way that they simulate the existing environment of the subjects. When performing the tasks, they could relate that to real situations in life. Even though we expect a tubular vision in advanced glaucoma, most of the patients were able to carry out daily activities such as ambulating, searching objects, reading, and recognizing easily. However, when it comes to fine activities such as telephoning, color matching, street sign recognition, and motion recognition, they are facing difficulty.

By performing the ADREV tasks, it becomes easy for the clinician as well as patient to assess the abilities and disabilities. It makes them aware of their capabilities, and at the same time, it warns them about their weakness. This helps in their lifestyle modification and thereby improving their QoL. Motion detection and street sign recognition were the parameters that were affected in all the three categories of glaucoma. Studies conducted by Richman and Spaeth *et al*. also showed the lowest score for motion detection.[10]

In a study conducted by Lin JC *et al*., most patients could walk without difficulty (76.4%), take care of themselves (89.6%), and

Table 1: Clinical characteristics of study population

Clinical characteristics	Mean	Range
Visual acuity (logMAR)	0.269	0-1
DDLS		
Better eye	5.49	1-10
Worse eye	6.72	1-10
Total ADREV score	52.59	31-63
Total NEI-VFQ-25 score	69.6	13.4-94.7
Pelli-Robson contrast sensitivity	0.978	0.15-2.25
Stereopsis	Present in 32 patients	

DDLS: Disc damage likelihood scale, ADREV: Assessment of disability related to vision, NEI-VFQ: National eye institute-visual functioning questionnaire, logMAR: Logarithm of the Minimum Angle of Resolution

Table 2: Correlation among study variables

Correlation between variables	ADREV score	VFQ score	Contrast (binocular)	Vision (logmar)	DDLS
ADREV score					
Pearson correlation	1	0.78**	0.53**	−0.56**	−0.61**
Significant (two-tailed)		0.000	0.000	0.000	0.000
n	100	100	100	100	100
VFQ score					
Pearson correlation	0.78**	1	0.58**	−0.46**	−0.54**
Significant (two-tailed)	0.000		0.000	0.000	0.000
n	100	100	100	100	100

**Correlation is significant at the 0.01 level (two-tailed). ADREV: Assessment of disability related to vision, VFQ: Visual functioning questionnaire, DDLS: Disc damage likelihood scale

manage activities of daily living without assistance (79.9%).[13] Our study also obtained similar results. The scores of individual tasks such as ambulation and navigation were significantly high in all the categories of glaucoma.

Contrast sensitivity

Glare, photophobia, poor contrast sensitivity, and light adaption are problematic for patients with advancing glaucoma. The value of assessing contrast sensitivity in a glaucoma screening may lie, first, in the positive correlation with both a large cup: Disc ratio and independently visual field loss. Second, in longitudinal studies of glaucoma suspects, progressive worsening of contrast sensitivity may possibly be a precursor of overt glaucomatous damage.[14]

The level of contrast sensitivity showed a decline as the stage of glaucoma advances, in our study, similar to studies by Richman *et al*. and Lorenzana *et al*.[15] Changes in contrast sensitivity, on the other hand, occur early and provide highly valuable insight into how well patients with glaucoma are able to function. In our study, a simple, quick method of assessing contrast sensitivity was used by asking patients to read letters of decreasing contrast in Pelli–Robson chart. In this study, contrast sensitivity was measured binocularly to simulate real life. It is seen that even in early stages, contrast sensitivity is low as compared to normal population similar to studies by Korth *et al*.[16]

Stereopsis

Gross stereopsis is another component of vision that is affected by glaucoma. In our study, there is a rapid decrease in the stereopsis with glaucoma progression similar to a study by Lakshmanan and George *et al*.[17] Decreased stereoacuity was associated with greater glaucomatous visual field loss, although it was normal with early visual field defects. Relatively moderate defects can be associated with decreased stereoacuity, and it is more pronounced in the severe stages of the disease when there is a threat to fixation.

CONCLUSION

1. ADREV (objective) scores correlate significantly with VFQ (subjective) scores in all the three categories of glaucoma
2. ADREV (objective test) scores correlate better with the severity and stages of glaucoma and degree of impairment patients experience than VFQ-25 (subjective test)
3. With respect to QoL, patients with glaucoma faced difficulty in performing fine tasks
4 However, even advanced glaucoma cases were able to carry out their daily activities without much help
5 Stereopsis and contrast sensitivity were the most affected with advancement of disease.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Comparison of applanation ultrasound biometry with optical biometry for intraocular lens power estimation in cataract surgery and their impact on prediction error

ABSTRACT

Aim: The aim of this study is to determine the agreement between applanation ultrasound biometry (AUB) and optical biometry using Lenstar 900 for precataract surgery axial length measurement and intraocular lens (IOL) power estimation and their effect on postoperative refractive outcomes. **Methods:** A case record-based retrospective study of 229 eyes which underwent phacoemulsification with foldable IOL, in a private hospital setting was done. All the eyes were evaluated using AUB and optical biometry for IOL power prediction. The IOL power was chosen based on the optical biometry and the final refraction was used to calculate the prediction error (PE) for both optical and ultrasound biometry. The concordance coefficient and Bland Altman's limits of agreement were determined to examine the disagreement between the two technologies. **Results:** The mean axial length ± standard deviation (SD) in the study eyes by ultrasound was 23.46 ± 1.01 mm and 23.57 ± 0.99 mm by optical biometry (P = 0.19). The axial length of 4.37% of eyes could not be measured by optical biometry. The mean IOL power prediction ± SD in the study eyes by ultrasound was 20.98 ± 2.68 D and 20.89 ± 2.85 D by optical biometry (P = 0.72). The mean ± SD absolute value of the refractive PE was 0.32 ± 0.44 D (median 0.25, interquartile range: 0.75–0). All eyes achieved a postoperative visual acuity of 6/18 or better including 204 (89.87%) that had a visual acuity of 6/6. One hundred and sixty-four eyes (71.62%) eyes had a postoperative spherical equivalent of 0 to ± 0.5D at 30 days. Two hundred and twenty eyes (96.07%) had a postoperative spherical equivalent of 0 to ± 1.0 D. **Conclusions:** The findings of the study prove that carefully done AUB is comparable to optical biometry and should not be a deterrent in providing the best possible refractive outcomes in a majority of our cataract patients. To ensure that these results are replicable on a wider scale will necessitate adequate training of personnel in the art and science of biometry.

Keywords: Intraocular lens power calculation, Lenstar 900, optical biometry, prediction error, ultrasound biometry

INTRODUCTION

Optical biometry and improved choices of formulas have changed cataract surgery from a predominantly sight-restoring surgery to a refractive surgery. However, refractive cataract surgeries are only a small proportion of the total cataract surgeries performed in India.[1,2]

A properly done ultrasound biometry provides good results with monofocal intraocular lenses (IOLs), which is the most frequently performed surgical procedure for sight restoration in age-related cataract.[2] Nearly 87% of patients can achieve a target postcataract surgery refraction within ± 1D, with proper selection of IOL power calculation formulas, good axial length measurements of the eye, and optimization of IOL constants.[3,4]

Norrby has previously reported on the influence of variability of input parameters on the refractive outcome and the final prediction error (PE).[5] Inaccuracies in axial

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length measurements can contribute up to 17% of the errors.[3,5] Optical biometry is the current gold standard for measuring axial length, however, a review of literature reveals that equivalence and not superiority has been established in most studies if actual visual outcomes are considered.[6,7] While this is true for eyes which fall within the normal range of anatomical parameters, eyes which are longer or shorter than normal do better with optical biometry, as do postrefractive surgery eyes and eyes with silicone oil.[8] Optical biometry has several disadvantages. About 10% to 15% of eyes cannot be measured with conventional partial coherence interferometry (PCI) technology[4,9] and about 2.42% of eyes cannot be measured due to dense opacities in the media even with the latest Swept-Source OCT-based biometers.[4] In addition to this, the cost of investment and maintenance of these machines are prohibitive and unaffordable for most hospital settings in India other than large corporate hospitals and Medical Colleges.

We designed a study to compare the concordance of optical coherence biometry (OCB) and contact or applanation ultrasound biometry (AUB) for the preoperative measurement of axial length and IOL power prediction before cataract surgery by phacoemulsification with foldable IOL implantation.

METHODS

The study protocol used a case record-based retrospective analysis that adhered to the tenets of the Declaration of Helsinki. The sample size for the study was estimated as 229 eyes based on a two-sided alpha of 0.05, a power of 90%, and a delta of 0.05. The case records of consecutive patients with age-related cataract who underwent standardized phacoemulsification with foldable IOL implantation by a single surgeon (MP) at the study institute between June 2019 and June 2020, were retrieved for the study. The study excluded patients with intra- or post-operative surgical complications, associated ocular pathologies such as zonular dialysis and posterior staphylomas, history of previous trauma or injuries to the eye, postrefractive surgery eyes, eyes with silicone oil, and patients requesting toric and multifocal IOLs.

All the patients were evaluated preoperatively by the surgeon MP. Preoperative assessment included uncorrected and best-corrected visual acuity, slit-lamp examination after dilatation of the eyes, IOP by applanation tonometry, and fundus evaluation with 90D lens. Biometry was done at least 2 days prior to surgery on pristine cornea before dilatation. Both AUB and OCB were performed by a single operator, the surgeon MP. The OCB was performed first followed by Manual Keratometry before instilling any drops in the eye. Following this, a drop of 0.5% proparacaine was instilled in the eye and AUB performed with special focus on the position of the probe in relation to the eye. Care was taken to align the probe with the visual axis. The output graph was given attention and only good quality scans were accepted for IOL power calculations. Optical biometry was performed using the Lenstar LS 900 (Haag Streit AG) following the manufacturer's recommendations. The Lenstar LS 900 is an optical biometer based on the principle of optical low coherence reflectometry. Manual keratometry was performed with the Appasamy Keratometer (Appasamy Associates, Chennai). AUB was done with the Echorule PRO Ultrasound Biometer (Biomedix Optotechnik and Devices, Bengaluru).

The target postoperative refractive status was emmetropia to −0.5 D myopia in all cases and the final IOL power selection was based on IOL power optimization and input from the optical biometer. The A Constant suggested by the IOL manufacturer was used to calculate the IOL power. The prediction by SRK/T formula was chosen as it is the most widely used IOL power estimation formula in practice today. Patients were operated by a 2.2 mm on axis limbal incision, 5 mm capsulorhexis, nucleus removal by phacoemulsification, and in the bag IOL implantation. Phacoemulsification was performed using catarhex phacoemulsification systems (Orteli. Switzerland). Three types of aspheric monofocal IOLs were used, Acrysof IQ (SN60WF), (Alcon, Fort Worth, TX. USA), Matrix Acrylic (403) (Medennium, Inc., Irvine California), and Technis (ZCB00) (Abbot Medical Optics, Illinois, USA).

Postoperatively, patients were examined at 1 day, 7 days, and 30 days after surgery. The objective refraction on the 13th day was collated from case sheets and converted to spherical equivalent for this study. The PE was calculated from the difference between the predicted refraction suggested by the instrument and the actual subjective postoperative refraction at 30 days.[10] The mean and median absolute value of the PE was estimated.

Lin's concordance correlation[11] coefficient for agreement on a continuous measure obtained by two persons or methods was used to determine the agreement between ultrasound and optical biometry for axial length and IOL power prediction. The concordance correlation coefficient combines measures of both precision and accuracy to determine how far the observed data deviates from the line of perfect concordance (i.e., the line at 45

degrees on a square scatterplot). Lin's coefficient increases in value as a function of the nearness of the data's reduced major axis to the line of perfect concordance (the accuracy of the data) and of the tightness of the data about its reduced major axis (the precision of the data). The Pearson correlation coefficient (r) is the measure of precision; the bias-correction factor is the measure of accuracy and the concordance correlation coefficient is expressed as the product of the measure of precision and the measure of accuracy. A concordance correlation coefficient <0.90 is considered as poor concordance, 0.90–0.95 as moderate, 0.95–0.99 as substantial, and 0.99 as almost perfect. The Bland and Altman's limits of agreement (LOA) were also determined to examine patterns of disagreement between the ultrasound and optical biometry measurements.[12] The correlation between difference and mean was also determined for the ultrasound and optical biometry measurements. A value near zero implies concordance.[13] The refractive PE was determined based on the postoperative spherical equivalent and the predicted spherical equivalent and the mean and median absolute value were estimated. At the study institute, the operating surgeon aims for a predicted spherical equivalent between 0 and −0.5D postoperatively and based it on the optical biometry measurements.

RESULTS

The study included 229 eyes that were assessed by ultrasound-based biometry and optical biometry. The mean age ± standard deviation (SD) of participants in the study was 66.30 ± 8.24 (median 67.00 years, interquartile range [IQR]: 61–72 years) and 116 (50.66%) were females. The study included 108 (47.16%) left eyes. The distribution of systemic and ocular comorbidity in the study population is presented in Table 1. Most of the operated eyes (n = 140, 61.14%) had a preoperative visual acuity of 6/24–6/60 [Table 2]. The mean axial length ± SD in the study eyes by ultrasound was 23.46 ± 1.01 mm and 23.57 ± 0.99 mm by optical biometry (P = 0.19). The axial length of 4.37% of eyes could not be measured by optical biometry and we used the axial length measured by US for further calculations. The mean IOL power prediction ± SD in the study eyes by ultrasound was 20.98 ± 2.68 D and 20.89 ± 2.85 D by optical biometry (P = 0.72). Table 3 presents the measure of concordance correlation coefficient for axial length and prediction of IOL power by ultrasound and optical biometry method in the study eyes. The concordance correlation coefficient of ultrasound and optical biometry for axial length and IOL power prediction was substantial for all preoperative visual acuity categories [Table 4]. The LOA, the mean difference, and the paired differences plotted against pair-wise means for axial length [Figure 1] and IOL power prediction was determined [Figure 2]. The mean ± SD absolute value of the refractive PE was −0.32 ± 0.44 D (median −0.25, IQR: −0.75–0). The mean ± SD absolute value of the refractive PE was −0.30 ± 0.48 D in the 54 study eyes with an axial length >24 and −0.34 ± 0.51D in the eight eyes with an axial length <22. All eyes achieved a postoperative visual acuity of 6/18 or better including 204 (89.87%) that had a visual acuity of 6/6. One hundred and sixty-four eyes (71.62%) eyes had a postoperative spherical equivalent of 0 to ± 0.5D at 30 days. Two hundred and twenty eyes (96.07%) had a postoperative spherical equivalent of 0 to ± 1.0 D. Sixty eyes (26.20%) had a postoperative spherical equivalent between −0.5D and −1.5D, and five (2.18%) eyes had a postoperative spherical equivalent between +0.5 D and +1.0D.

DISCUSSION

Cataract extraction with IOL implantation is the commonest surgical procedure performed in India. AUB is the most

Table 1: Systemic and ocular comorbidity in the study population

Comorbidity	*n* (%)
Diabetes	96 (41.92)
Hypertension	129 (56.33)
Thyroid disorders	33 (14.41)
Dyslipidaemia	87 (37.99)
Corneal disorders	7 (3.06)
Glaucoma	7 (3.05)
Retina	14 (6.11)

Table 2: Distribution of preoperative visual acuity in the study eyes

Preoperative visual acuity	*n* (%)
6/6-6/18	46 (20.09)
6/24-6/60	140 (61.14)
Worse than 6/60	43 (18.78)

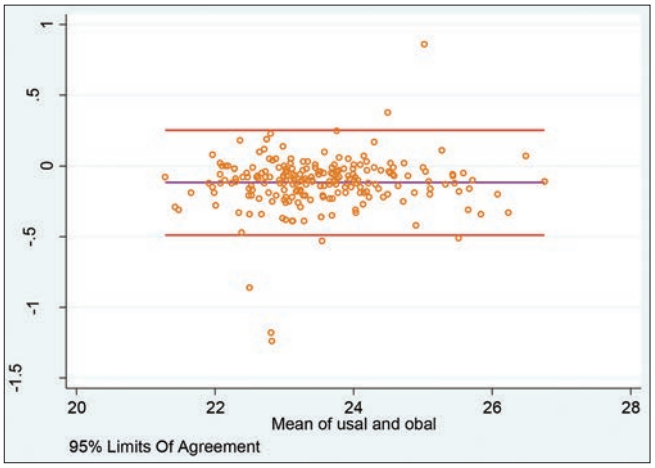


Figure 1: Limits of agreement between the ultrasound and optical biometry assessment of axial length

common technique used to measure the axial length of the eye for calculation of IOL power.[14] However, there is a general belief that optical biometry provides superior and more accurate IOL power prediction when compared to ultrasound biometry. Several studies have reported equivalence in postoperative refractive outcomes when the two technologies are compared.[7,15,16]

Previous studies have reported that optical biometry measurements cannot be estimated in approximately 10% of cases.[7,14] We could not measure the axial length using optical biometry in 4.37% of eyes in this study. The reason for this could be that dense cataracts were lesser in this study (preoperative visual acuity was <6/60 in 43 [18.78%] patients). Many of the studies comparing optical biometry with ultrasound biometry were designed to include only those cases in which optical biometry measurements were possible and this leads to a bias toward optical biometry.[15-17]

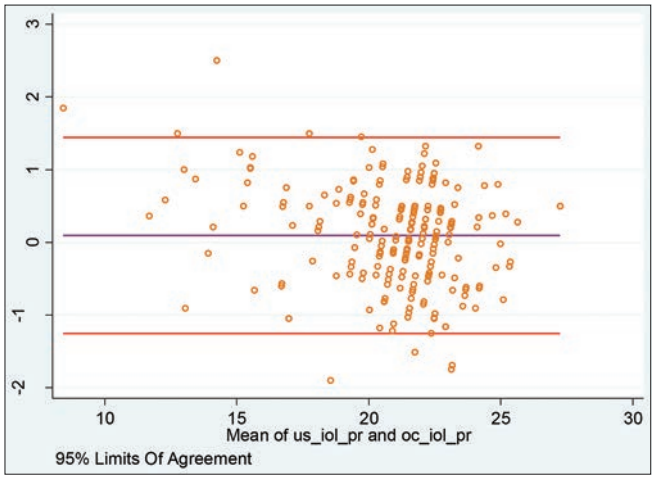


Figure 2: Limits of agreement between the ultrasound and optical biometry assessment of intraocular lens power prediction

This issue has been well documented by Raymond *et al.* who states that, "A group analysis that excludes PCI failures may cause serious bias and overestimate clinical effectiveness of the outcome measures."[7] The negative fallout of such a narrative is that ophthalmic centers are pushed into investing in a technology that does not offer tangible advantages for most patients compared to a tried and tested cheaper technology. The shift toward optical biometry has also led to laxity in training for good ultrasound A scan techniques, as the accuracy of A scan is highly dependent on obtaining a proper scan along the optical axis. A recent study that compared applanation biometry, immersion biometry, and optical biometry with IOL Master reported that only 46.4% of eyes were within ± 1 D with applanation biometry[18] and possibly demonstrates a lack of procedural or technical skill as all previous studies have shown far superior results in the range of 70.0% to 89.4%.[7,19]

The results of our study show comparable results for the measurement of axial length and IOL power calculation by ultrasound and optical biometry. The difference was not clinically significant as the effect of such a small difference (0.11 ± 0.02 mm) on IOL power calculation is negligible. Most (96.07%) of our patients achieved a postoperative spherical equivalent of 0 to ± 1.0 D and 71.62% achieved a spherical equivalent of 0 to ± 0.5 D. These results are comparable to outcomes in previous studies[7,19,20] and support the good postoperative results of both AUS and OCB in IOL power calculation.

Several studies have compared immersion ultrasound biometry with optical biometry and found that the results are comparable.[8,9,21] Immersion biometry has also been compared to contact biometry and found to have similar results in a study by Hennessy *et al*.[22] Immersion biometry is

Table 3: Concordance correlation coefficient for axial length and intraocular lens power prediction by ultrasound and optical biometry

	Axial length by ultrasound and optical biometry	IOL power by ultrasound and optical biometry
Pearson correlation coefficient	0.982	0.971
Bias correction factor	0.993	0.998
Concordance correlation factor (95% CI)	0.975 (0.969-0.982)	0.969 (0.961-0.976)
Bland-Altman 95% limits of agreement	−0.48 (0.22)	−1.256 (1.442)
Difference mean correlation	0.07	0.24

IOL – Intraocular lens, CI – Confidence interval

Table 4: Concordance correlation coefficient of ultrasound and optical biometry for axial length and intraocular lens power prediction by preoperative visual acuity

Preoperative visual acuity	Concordance correlation coefficient (95% CI)	
	Axial length	IOL power prediction
6/6-6/18	0.964 (0.943-0.983)	0.954 (0.928-0.980)
6/24-6/60	0.982 (0.976-0.988)	0.970 (0.961-0.980)
Worse than 6/60	0.959 (0.932-0.985)	0.970 (0.952-0.987)

IOL – Intraocular lens, CI – Confidence interval

theoretically more accurate but is rarely done due to technical difficulties in doing the procedure. It is also a messier process as it involves using a Prager shell filled with saline to be placed on the eye which is anesthetized prior to the procedure. Therefore, it was important to compare the commonly done contact or AUB with optical biometry to get a pragmatic idea of the real situation in clinical practice. Most studies were prospective with two cohorts assigned to either ultrasound biometry or optical biometry and doing a comparative study, instead of measuring the same eyes with both the technologies simultaneously.[7,15] This introduces avoidable errors and biases in patient selection and outcomes.[7]

The agreement between various types of optical biometry using different principles such as PCI, optical low-coherence interferometry, and swept-source OCT has been amply demonstrated by various studies.[4,19] Hence, it is reasonable to assume that the results of our study demonstrated with the Lenstar 900 can be extrapolated to other optical biometers with a similar degree of confidence. It is also interesting to note that unlike many studies we do not see significant difference in PEs between AUB and OCB in long and short eyes. However, as the number of cases of these outliers are less in this study, it may not feasible to draw definitive conclusions about these types of eyes without further research.

There is a definite space for optical biometry in the cataract surgery armamentarium, especially when dealing with postrefractive surgery eyes, premium IOLs, postvitrectomy, and silicone oil-filled eyes. However, to mandate the requirement of optical biometry for achieving good refractive results in all cataract surgery is not necessary. This is especially true in a country such as India where we have a wide range of clinical settings from the resource-poor rural hospitals which service a majority of our population to the large well-equipped hospitals in urban spaces. Wherever feasible it is advisable to have an optical biometer for IOL power calculations as inter-operator variability of these machines are minimal.[23] Hence, the major advantage is that resources spent on operator training can be minimized and hospitals with large turnover of patients will definitely benefit by giving consistent results with optical biometer. In contrast, the variability between an expert biometrist and a nonexpert operator in ultrasound biometry can be up to ten times when compared to optical biometry as shown by Goel *et al*.[24]

However, this cannot be a reason for poor refractive outcomes in cataract surgery for a large majority of our patients who do not have access to larger hospitals with the latest equipment. The reason for choosing ±1 D of postoperative PE as acceptable is because the patient can generally see well without glasses in this range. Anything beyond 2 D is a situation of unacceptable refractive error necessitating further interventions. An ultrasound biometer costs only one-tenth of the cost of an optical biometer and is invariably available in all types of surgical centers doing cataract surgery. Citing the lack of an optical biometer due to fiscal hurdles, for poor refractive outcomes cannot be acceptable in any kind of setting. This is what we have tried to demonstrate in this study. Giving sufficient training to optometrists and ophthalmologists to do a good ultrasound A scan can ensure that >90% of our patients achieve target refraction of ±1 D after cataract surgery. A system of performance audits and programs for skill enhancement training can optimize biometry results. Optical biometry will still be needed for patients with long or short eyes, postrefractive surgery eyes, and other situations listed earlier. Most of our towns and cities have multiple ophthalmic centers with this expensive equipment. A system of group practice or limited referral system can be arranged for patients for whom optical biometry is mandatory. However, the larger majority of patients can be managed efficiently with careful AUB.

The single operator measurements, surgery, and documentation are the strengths of this study. The retrospective nature of the study maybe considered a limitation. The surgeon was not masked to the results of the optical biometry and this may possibly have introduced a bias in the ultrasound measurements and the estimation of the final IOL power that was eventually used. The single center nature of the study can introduce selection bias and is another limitation. Further prospective studies from diverse medical settings can help to determine if the concordance between US biometry and optical biometry remains high in all situations.

CONCLUSIONS

This study has demonstrated the feasibility of achieving excellent postoperative refraction after cataract surgery using the IOL power predicted by optical biometry and ultrasound biometry. As the results from both technologies were closely matched, an argument for choosing ultrasound biometry without compromising on refractive outcomes can be made, especially for settings with fiscal disadvantages. However, it has to be emphasized that operators of ultrasound biometry have to be adequately trained and their performance periodically audited for optimum and consistent results.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Evaluation of retinal changes in normal pregnancy and gestational hypertension – A spectral domain optical coherence tomography based study

ABSTRACT

Background and Objectives: Hypertensive disorders complicating pregnancy is a complication of pregnancy, which includes gestational hypertension, preeclampsia and eclampsia syndrome, preeclampsia superimposed on chronic hypertension, and chronic hypertension of any etiology. The pathogenesis of the first three and last two varies. The present study focuses on the first three categories of patients. Optical coherence tomography (OCT) is a noninvasive medical imaging modality used for *in vivo* visualization of retinal layers in human eyes. This study analyzed the retinal thickness changes in patients with gestational hypertension and compared it with normal pregnant study participants. Furthermore, the duration of gestational hypertension with changes in retina was compared. **Materials and Methods:** A comparative study was performed in 206 patients (103 normal pregnant and 103 gestational hypertensive patients). Macular thickness in nine segments and ganglion cell inner plexiform layer thickness (GC-IPL) in six sectors were assessed using cirrus high-definition OCT and compared between two groups. The study period was 18 months. **Results:** Among the 412 eyes in two groups, there was a statistically significant increase in macular thickness in six segments in the gestational hypertension group compared to the healthy pregnant group ($P < 0.05$). A statistically significant positive correlation was found between macular thickness and duration of hypertension in two segments and a negative correlation between the GC-IPL thickness in two sectors and duration of hypertension was observed ($P < 0.001$). **Conclusion:** Spectral-domain OCT can be used for detecting early retinal changes in gestational hypertension before any clinical signs appear.

Keywords: Ganglion cell inner plexiform layer, gestational hypertension, macular thickness, optical coherence tomography

INTRODUCTION

Gestational hypertension is diagnosed when there is blood pressure >140/90 mmHg after 20 weeks of pregnancy in a previously normotensive woman.[1] The main clinical manifestations of gestational hypertension include rapid or sudden weight gain, high blood pressure, protein in the urine, swelling (hands, feet, and face).[2] Retinal vessels are the only body parts of which vascular changes can be directly observed *in vivo*, and fundus examination was the principal criterion to evaluate the development of the degree of gestational hypertension during the early years.[3]

Optical coherence tomography (OCT) has found wide application in ophthalmology in recent years. It is based on low coherence interferometry. With OCT, multiple thin slices of the retina can be obtained; laminar sheet structural images of morphologic changes of the retina including vitreomacular

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traction, diffuse thickening, intraretinal cystic changes, subretinal fluid can easily be detected.[4]

This study emphasizes on retinal thickness changes in patients with gestational hypertension and compares it with normal pregnant study participants and also compares the duration of hypertension with the OCT changes.

MATERIALS AND METHODS

This comparative study was conducted in the Department of Ophthalmology and Obstetrics and gynecology in a tertiary care center in Kerala from January 2019 to June 2020 and included 206 patients. Patients diagnosed with hypertension after 20 weeks of pregnancy from the Department of Obstetrics and Gynaecology were included in the study except for those patients where an OCT could not be taken, patients with other pregnancy complications that would affect the study outcome, patients on drugs that affect the retinal thickness, patients with preexisting retinal pathologies, intraocular pressure >21 mm Hg, patients with chronic hypertension and preeclampsia complicated by chronic hypertension, patients diagnosed with hypertension before 20 weeks of pregnancy and patients who had undergone previous intraocular or refractive surgeries. This was compared with normal age-matched healthy pregnant participants.

The patients were enrolled in the study after taking informed consent. Gestational hypertensives were considered as Group 1 while healthy pregnant participants as Group 2. A detailed history about any previous or existing ophthalmic diseases, surgeries, or co-existing medical or surgical conditions was taken. Ophthalmologic examination including visual acuity, slit-lamp examination, intraocular pressure (IOP) measurement and fundus evaluation was done and documented. OCT using cirrus high-definition OCT without pupillary dilatation and under the same intensity of dim room lighting was done and the following parameters evaluated:

1. Macular thickness measured in fovea, superior inner, inferior inner, nasal inner, temporal inner, superior outer, inferior outer, nasal outer, and temporal outer fields
2. Ganglion cell layer with inner plexiform layer thickness was measured in super nasal, infer nasal, superotemporal, inferotemporal, superior, and inferior sectors.

Values were compared with normal age-matched pregnant study participants.

Based on the mean and standard deviation of the foveal center observed in an earlier publication by "Atas *et al*.,"[5] with 95% confidence level and 80% power minimum, the sample size was found to be 103 in each group.

Numerical variables were expressed as either mean and standard deviation or median and IQR. Categorical variables were represented by frequency and percentage analysis. To compare retinal and ganglion cell inner plexiform layer thickness (GC-IPL) thickness between two groups Mann–Whitney U test was used. Karl Pearson's coefficient of correlation was used to find out the correlation macular and GC-IPL thickness with study variables. P value < 0.05 was considered statistically significant. Data obtained from 206 patients were coded and entered into Microsoft Excel sheet using SPSS version 25 (IBM, Armonk, NewYork, USA).

RESULTS

Age distribution

The mean age in the gestational hypertension group was 28.52 years whereas in the normal pregnant group it was 27.03 years with $P = 0.068$. Since P value is > 0.05 the age between the two groups are comparable. The age group of patients in both the group ranges from 18 to 45 years. The youngest patient in the study was 19 years old [Figure 1].

Retinal thickness analysis between gestational hypertension and healthy pregnant

Both macular and ganglion cell layer thickness was analyzed in 412 eyes

Macular thickness analysis

All the ETDRS segments showed an increase in macular thickness in the gestational hypertensive group compared to the healthy pregnant group.[Figure 2] A statistically significant increase in thickness was found in the foveal center, superior inner, inferior inner, inferior outer nasal outer, and temporal outer macula ($P < 0.05$) [Figure 3a and b].

Ganglion cell inner plexiform layer thickness

All the 6 sectors of GCIPL thickness showed thinning in the gestational hypertension group with the superotemporal

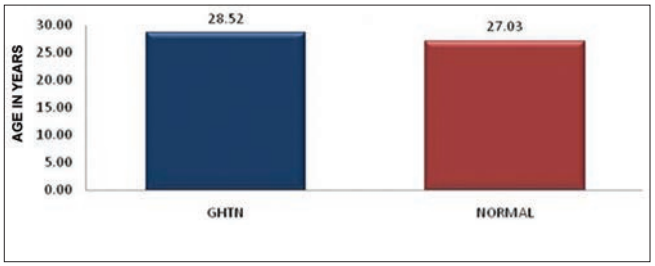


Figure 1: Comparison of age between gestational hypertension and normal pregnant study participants

sector showing maximum thinning in both groups. Maximum thickness was noted in the superonasal sector in the gestational hypertension group and in the inferior sector in the normal healthy pregnant group. Minimum GC-IPL thickness showed a significant thinning in the hypertensive group compared to the healthy pregnant group ($P < 0.05$) [Figure 4].

Intraocular pressure between two groups

IOP was analyzed in both groups, i.e., a total of 412 eyes. Both groups showed a normal IOP and the IOP among the healthy pregnant group was increased compared to the gestational hypertension group [Figure 5].

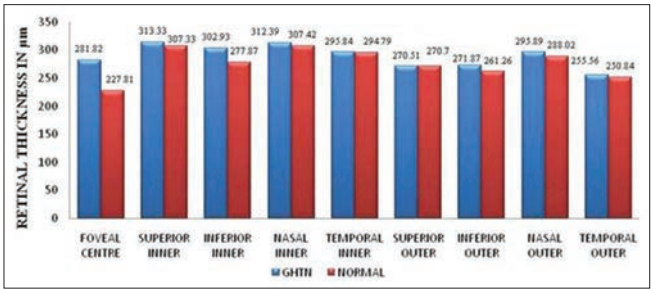


Figure 2: Macular thickness analysis between gestational hypertension and healthy pregnant women

Correlation of macular and ganglion cell inner plexiform layer thickness thickness with the duration of gestational hypertension

A statistically significant positive correlation was found between the superior and temporal outer macular thickness and duration of hypertension ($P < 0.001$) [Table 1]. Also, a statistically significant negative correlation between the GC-IPL thickness in the superotemporal and inferonasal sector and duration of hypertension was observed ($P < 0.001$) [Table 2].

Table 1: Correlation of macular thickness with duration of hypertension

ETDRS segment	Duration of HTN (weeks)		
	n	Correlation coefficient	*P*
Foveal center	206	0.15	0.031
Superior inner	206	0.133	0.057
Inferior inner	206	0.059	0.404
Nasal inner	206	0.205	0.003
Temporal inner	206	0.182	0.009
Superior outer	206	0.312	<0.001
Inferior outer	206	0.231	0.001
Nasal outer	206	0.072	0.303
Temporal outer	206	0.294	<0.001
Average thickness	206	0.175	0.012

HTN – Hypertension, ETDRS – Early Treatment Diabetic Retinopathy Study

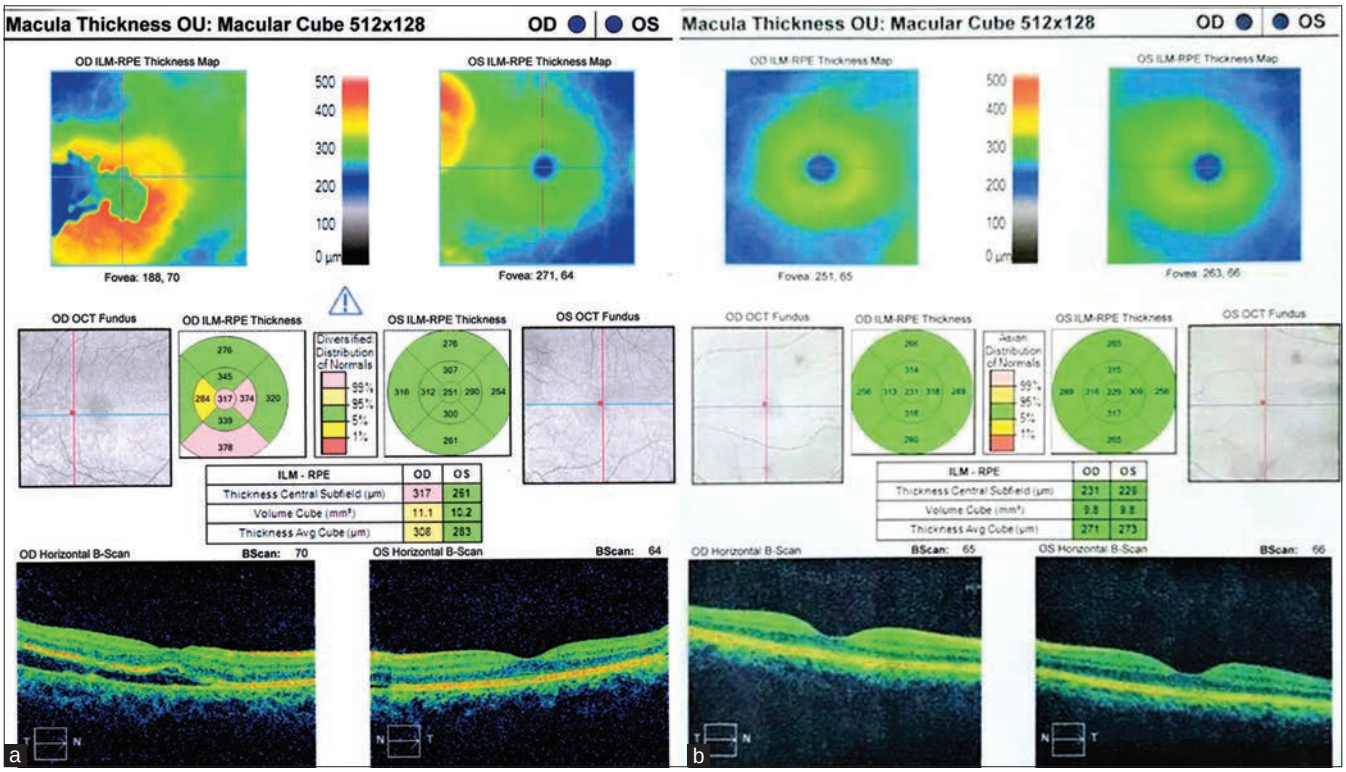


Figure 3: (a) Optical coherence tomography macula of group 1 patient showing increase in thickness in foveal centre, nasal inner, nasal outer and inferior outer macula. (b) Optical coherence tomography macula of group 2 showing normal macular thickness

DISCUSSION

The study was a comparative study conducted in 412 eyes of 206 patients of which 103 were gestational hypertension patients and 103 were healthy pregnant women. All patients attending the Obstetrics and Gynaecology department at a tertiary care center in Kerala coming under the inclusion criteria were enrolled for the study.

Comparison of age

Patients were aged between 18and 45 years. The mean age in the gestational hypertension group was 28.52 years whereas in the normal pregnant group it was 27.03 years with $P > 0.05$ indicating the two groups were comparable. Statistical analysis showed that there was no significant correlation of age between the two groups. Eriksson *et al*.[6] conducted a study that proved that macular thickness decreases in all ETDRS segments with age. However, a study done by Xu *et al*.[7] proved that there was no significant change in foveal thickness with age, but the GCIPL thickness reduced with age. In this study, there was no correlation between age and macular thickness. The youngest study participant was 19 years old and the eldest 41 years.

Comparison of macular thickness

Among the 412 eyes divided between the two groups, there was an increase in macular thickness in 8 quadrants in the gestational hypertension group except in the superior outer macula which showed no change between the two groups. However statistically significant increase in macular thickness was observed in the foveal center, superior inner, inferior inner, inferior outer nasal outer, and temporal outer macula ($P < 0.05$) in the gestational hypertensive group.

The study conducted by Atas *et al*.,[5] showed that macular thickness decreased in the preeclampsia group when compared to the healthy pregnant group in all quadrants but statistically significant thinning was found only in the foveal center. This deferred from our study where it was observed that there is the increase in macular thickness in gestational hypertension when compared to healthy pregnant patients except in the superior outer macula which showed no change between the 2 groups. In a study by Demir *et al*.,[8] it was found that foveal and parafoveal retinal thickness were increased, particularly in the last trimester and this increase was attributed to the pregnancy-related fluid retention in the retinal tissue.

The thickness of the 9 ETDRS segments was analyzed and compared with studies conducted by Atas *et al*. and Demir *et al*. and Wu *et al*.[9] [Table 3].

When macular thickness in gestational hypertension was compared between our study and other similar studies, it was found that the thickness was less in our study in all quadrants

Table 2: Correlation of ganglion cell inner plexiform layer thickness with duration of hypertension

Sectors	Duration of HTN (weeks)		
	n	Correlation coefficient	*P*
Superior	206	−0.228	<0.001
Superonasal	206	−0.035	0.617
Inferonasal	206	−0.367	<0.001
Inferior	206	−0.037	0.598
Inferotemporal	206	−0.073	0.300
Superotemporal	206	−0.247	<0.001
Average GCIPL	206	−0.141	0.043
Minimum GCIPL	206	−0.187	0.007

GCIPL – Ganglion cell inner plexiform layer, HTN – Hypertension

Table 3: Comparison of macular thickness with other studies

ETDRS segments	Present study	Atas *et al*.	Wu *et al*.
Foveal centre	281.82±45.18	211.09±12.93	287.36±7.33
Superior inner	313.33±17.59	342.23±11.53	323.71±10.62
Inferior inner	302.93±33.19	336.23±11.84	319.93±9.00
Nasal inner	312.39±27.18	331.96±13.87	323.29±8.68
Temporal inner	295.84±33.25	331.42±14.15	306.86±9.03
Superior outer	270.51±23.40	299.62±12.12	283.36±9.15
Inferior outer	271.87±39.14	290.47±11.62	268.08±8.40
Nasal outer	295.89±24.38	299.6±20.83	302.93±7.99
Temporal outer	255.56±19.67	300.47±21.08	259.64±10.57

ETDRS – Early Treatment Diabetic Retinopathy Study

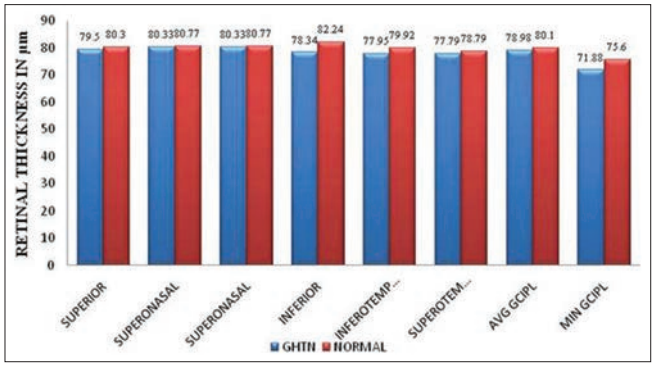


Figure 4: Ganglion cell inner plexiform layer thickness thickness analysis between GHTN and healthy pregnant women

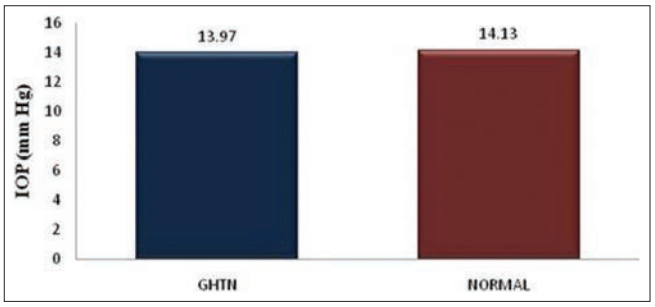


Figure 5: Analysis of intraocular pressure between GHTN and normal groups

except the foveal center as compared to the study by Atas *et al*.[5] Whereas when compared with the study by Wu *et al*. thickness in all quadrants were decreased except the inferior outer macula.

Macular thickness in healthy pregnancy was compared with similar studies and it was found that retinal thickness was less on our study in all quadrants except foveal center compared to study by Atas *et al*. and it was less in all quadrants in our study compared to that by Demir *et al*.

Comparison of Ganglion cell-inner plexiform layer thickness

The GC-IPL thickness in each of the 6 sectors was compared between healthy pregnant and gestational hypertension groups and it was found that the GCIPL thickness was reduced in all sectors in patients in gestational hypertension compared to the healthy pregnant group. However, statistically significant reduction was not seen between the two groups even though the minimum GC-IPL thickness showed a statistically significant thinning in our study ($P < 0.05$).

A study conducted by Lee *et al*.[10] proved that patients with hypertension exhibited a significant reduction in GC-IPL thickness. Tok *et al*.[11] compared antenatal and postpartum OCT findings of ganglion cell density in preeclampsia patients and healthy pregnant women. No statistically significant difference was obtained between the groups in respect of retinal ganglion cell density.

The study by Gooding *et al*.[12] postulated that pregnancy itself has an up-regulated inflammatory response associated with it. In addition to this patients with hypertension in pregnancy will have an exaggerated inflammation which may lead to loss of endothelial integrity. This causes a decrease in colloid osmotic pressure and extravascular fluid retention. Retinal changes in preeclampsia may be due to a complex interaction between choroidal ischemia, due to vasoconstriction, and endothelial dysfunction with the leakage of proteins, subsequent edema, and formation of exudative retinal detachments. None of the patients showed fundus changes except one patient with eclampsia who had hypertensive retinopathy changes. Hence, it may be hypothesized that the retinal thickening may be the precursor for the hypertensive changes to occur clinically.

Intraocular pressure changes in pregnancy

Analysis of IOP recorded with Goldmann Applanation Tonometry revealed a mean IOP of 13.97 ± 2.59 in the gestational hypertension group and 14.13 ± 2.65 in the healthy pregnant group ($P > 0.05$). According to our study, the IOP had a small increase in the healthy pregnant group compared to hypertensive patients which were not statistically significant. Tolunay *et al*.[13] conducted a study on IOP changes in different trimesters of pregnancy which showed that mean IOP was 13.9 ± 1.6 mm Hg in both eyes in the third trimester. Also, a decline in the IOP was observed from 1st to 3rd trimesters in pregnancy. Midha *et al*. reported that mean IOP at the third trimester normotensive pregnant women (11.9 mmHg) was almost similar to that of patients of pregnancy-induced hypertension (12.1 mmHg), thereby suggesting that the factors responsible for lowering the IOP, are independent of blood pressure. No studies have compared the IOP between gestational hypertension and normal pregnancy.

IOP lowering in pregnancy is caused by placental hormones, estrogen, relaxin, and progesterone mediated vasodilatation. This results in decreased IOP with the progression of pregnancy.[14]

Correlation of macular and ganglion cell inner plexiform layer thickness thickness with the duration of gestational hypertension

A statistically significant positive correlation was found between the superior and temporal outer macular thickness and duration of hypertension ($P < 0.001$). However, the average macular thickness did not have any significant correlation with the duration of hypertension. There wasn't any similar study in the literature comparing the duration of hypertension and its association with OCT changes.

A statistically significant negative correlation between the GC-IPL thickness in the superotemporal and inferonasal sector and duration of hypertension was observed in our study indicating that with the increasing duration of hypertension there was a decrease in the GC-IPL thickness in the above-mentioned sectors ($P < 0.001$). Also, there was a decrease in average GC-IPL thickness with increasing duration even though it was not statistically significant. Tabaczi *et al*.[15] reported that the duration of hypertension had a weak negative correlation with GC-IPL thickness in the superotemporal, inferonasal, and inferotemporal GC-IPL in DM patients. Also, hypertension had a weak relationship with only the inferonasal sector in healthy patients.

CONCLUSION

The study was conducted among 412 eyes of 206 patients and the results were compared between the group with gestational hypertension and the healthy pregnant group. The average age distribution in the gestational hypertensive group was 28.52 years whereas in the healthy pregnant group was 27.03 years. OCT macula showed a statistically significant increase in thickness in patients with gestational hypertension in the foveal center, superior inner, inferior

inner, inferior outer nasal outer, and temporal outer macula compared to the healthy pregnant group. GC-IPL thickness was decreased in the gestational hypertension group compared to the healthy pregnant group but statistically significant thinning was not present. However, the minimum GC-IPL thickness showed statistically significant thinning in the hypertensive group. Significant positive correlation was present between the duration of hypertension and macular thickness in superior and temporal outer segments. Also, a significant negative correlation was present between GC-IPL thickness in superotemporal and inferonasal sectors and duration of gestational hypertension.

Hence, it can be concluded that spectral-domain OCT can be used as a screening tool to detect changes in the retina in gestational hypertension before the appearance of clinical signs. It can be used for detecting retinal changes in these patients before vision-threatening complications occur.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Awareness of retinopathy of prematurity screening among healthcare professionals in Palakkad district of Kerala

ABSTRACT

Purpose: To understand the level of knowledge and create awareness about retinopathy of prematurity (ROP) among Pediatricians, General Practitioners, and Paramedical staff in the Palakkad district. **Materials and Methods:** A Questionnaire with multiple choice answers, created to determine the knowledge and current practices of ROP screening, was administered to 216 participants including 97 Pediatricians, 61 General Practitioners, and 58 Paramedical staff (staff nurses and optometrists) in a period of 1 year. The responses were collected and analyzed. **Results:** Most respondents (70.7%) were from the public sector. More than 90% of respondents in the three groups reported awareness of ROP as a preventable disease in premature babies. However, the knowledge of screening criteria and timing of screening was poor among all participants including Pediatricians. The awareness and knowledge did not differ significantly by respondents in the public and private sector (all $P > 0.05$). **Conclusion:** There is an urgent need to focus on strategies to increase awareness of the timing and criteria for the screening are suboptimal even among Pediatricians.

Keywords: Awareness, retinopathy of prematurity, screening criteria

INTRODUCTION

Retinopathy of prematurity (ROP) is an important cause of preventable blindness in children. An estimated 14.9 million children are born preterm (earlier than 37 weeks of gestation) worldwide[1] and nearly 1,84,700 these preterm children develop any stage ROP.[2] Approximately 32,000 children worldwide were reported to have severe visual impairment attributed to ROP in 2010.[2] India has a high incidence of preterm births with an estimated 3.7 million preterm births in 2010.[2] India contributes an estimated 10% of the global prevalence of blindness and visual impairment due to ROP with at least 5,000 developing severe disease and 2,900 children surviving with visual impairment related to ROP in 2010.[3,4]

Middle-income countries, like India, are experiencing the "third global epidemic" of ROP due to factors that include better survival of preterm babies and inadequate access to quality neonatal care.[4] Estimates of ROP in India were previously limited to urban neonatal units with the reported incidence varying from 37% to 54% in neonatal units.[5,6] However, improving survival rates of preterm children has led to the identification and reporting of ROP from semi-urban and rural units of Southern India with estimates of ROP that vary from 22.4% to 41.5% in neonatal units.[7-9] ROP, if left untreated, causes bilateral retinal detachment and permanent and total blindness. Blindness in a child can lead to economic, social, psychological, educational, and employment potential losses and can affect the individual child and their family. A previous study from India reported that the fiscal quantum of blind person-years saved is approximately 108.4 million

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USD annually if ROP screening is standardized and expanded across India.[10]

Babies with ROP are not born blind and there is a time interval between the occurrence of stage 1 ROP and threshold ROP that needs treatment. However, ROP can be treated successfully, only if detected at the right time. Timely screening and detection of ROP at the correct time can save the vision and change the life of the child. Childbirth in Kerala is primarily institutional and hence the possibility of early screening and intervention for ROP is high. We designed a cross-sectional study to explore prevailing knowledge, attitudes, and practice related to ROP among Pediatricians, General Practitioners, and Paramedical Staff involved in Neonatal care at Palakkad District in Central Kerala.

MATERIALS AND METHODS

A seven-item closed-ended questionnaire in the English language was developed to collect information including the setting of practice (private or public sector) and specialization of respondents, and awareness of ROP, if blindness in ROP is preventable, the timing of screening for ROP, which babies must be screened, the modality of screening, if ROP is treatable and modalities of treatment for ROP. Individual demographic details including age and gender or name were not collected from respondents. The questionnaire was distributed to the pediatricians as part of a conference on pediatrics held at the Study District in 2018 and to the general practitioners in the public sector as part of a health services conference held in the study district in 2018. The questionnaire was given in person to the paramedical staff (Staff nurses and optometrists in the Government hospitals of the study district) in 2018 and responses were collected in person. Data from the study forms were entered in an MS Excel spreadsheet. The distribution of responses is presented as a proportion by groups.

RESULTS

The study included 216 participants including 97 (44.91%) pediatricians, 61 (28.24%) general practitioners and 58 (26.85%) paramedical staff. Most respondents (n = 152, 70.7%) were from the public sector and 64 (29.63%) were from the private sector.

The awareness of ROP, that blindness from ROP is preventable and screening processes were high among the study respondents [Table 1]. However, knowledge of screening criteria, the timing for screening and treatment modalities of ROP was suboptimal in the study respondents [Table 1]. The awareness of the screening criteria for ROP was 70% among general practitioners and 80% in pediatricians. Nearly three-fourth of the general practitioners and paramedical staff were not aware of the appropriate time for ROP screening. The awareness of treatment modalities was nearly similar for pediatricians and general practitioners [Table 1]. Lasers were considered the only available treatment option for ROP by 19.64% of general practitioners and 26.04% of pediatricians. The distribution of responses did not differ significantly by respondents in the public or private sector (all $P > 0.05$).

DISCUSSION

The district of Palakkad in central Kerala is a predominantly rural district with a high literacy rate. Most childbirths are institutional in the district like other parts of Kerala. However, the district has only a few specialty hospitals that offer state-of-the-art neonatal care. Preterm babies are always under the care of a pediatrician or neonatologist in the study district and the knowledge, awareness, and involvement of pediatricians and neonatologists in the screening of ROP is important. The suboptimal levels of awareness on screening criteria, the timing of screening, and possible modalities of treatment among respondents indicate the need for more sustained educational programs on ROP in the study district.

Previous studies have reported poor awareness of ROP among pediatricians in several countries of Asia, Africa, and the Middle East.[11-15] Previous studies have reported on awareness of ROP among pediatricians from different parts of India with higher awareness reported from metropolitan cities. High awareness of the risk factors for ROP was reported from Hyderabad (100%) and Pune (80%) but was much lower (57.8%) among pediatricians at a tier two city in south India.[16,17] The awareness of ROP (98%) in our study is consistent with reports from Hyderabad and Pune. The awareness of ROP was similar among pediatricians, general practitioners, and paramedical staff in the study and indicates widespread awareness of ROP in the healthcare practitioners of the district.

However, we found that awareness of screening guidelines, the timing of screening, and modalities of treatment were suboptimal in our study. These results are consistent with previous studies from India and other parts of the world.[11-17] Awareness of the screening criteria ranged from 70% among general practitioners to 80% among pediatricians in our study. Awareness of the modalities of treatment was 69.64% among general practitioners and 70.73% among pediatricians. Awareness of the timing of screening was only 23.33% among general practitioners and 60.82% among pediatricians. The high awareness of ROP but suboptimal awareness of the management modalities indicates the possible presence of

Table 1: Outcome of analysis

	Pediatricians (%)	General practitioners (%)	Paramedical staff (%)
Total participated	97	61	58
Awareness of ROP	96 (98.97)	60 (98.36)	57 (98.28)
Understanding ROP is preventable	93 (95.88)	58 (95.08)	53 (92.98)
Knowledge of screening criteria	78 (80.41)	42 (70)	41 (74.55)
Knowledge of time of screening	60 (61.85)	14 (23.33)	15 (26.79)
Knowledge of screening procedure	88 (93.62)	59 (98.33)	50 (89.29)
Knowledge of treatment	68 (70.83)	39 (69.64)	45 (83.33)

ROP Retinopathy of prematurity

a gap between awareness and its translation to practice. These results have implications for the success of the ROP program in the district as screening and management at the appropriate time intervals is necessary to prevent blindness from ROP.

Screening guidelines, criteria, and management modalities in developed countries recommend screening babies ≤30/32 weeks or ≤1500 g.[18-20] However, ROP is not restricted to smaller preterm babies in India and these guidelines must be adapted for use in India. Pediatricians and general practitioners must be made aware that larger and more mature babies are at risk of developing vision-threatening ROP in India due to the wide variation in the standard of neonatal care.[21-23] The revised guidelines for ROP in India recommend screening all babies with birth weight <2000 g or gestational age <34 weeks or infants with unstable clinical course who are determined by the neonatologist or pediatrician to be at high risk for ROP.[24] It is recommended to undertake the first ROP screening session before "day 30" of life and by "day 20" of life in smaller babies (possibly <30 weeks and/or birth weight <1200 g).[25] A previous study has reported that lower target oxygen saturations are protective and monitoring should aim to keep oxygen levels between 83% and 93% and not higher.[26,27] Improved awareness of screening criteria and guidelines is important as a previous study reported that only 14.5% of pediatricians followed standard guidelines.[28]

Appropriate screening and care for ROP is a legally mandated requirement in India.[10] The neonatologist or pediatrician at the neonatal care units is important to ensure appropriate screening for ROP in babies. It is also important that general practitioners and family physicians are aware of the screening guidelines and timing, especially in areas where there are fewer neonatal support services. It is also important to train more ophthalmologists to manage ROP in India. There are <200 ophthalmologists trained to manage ROP in India at present[4] and more training programs are essential to cover many babies at risk for ROP in India.

Our study has several limitations. The self-selection of participants attending conferences is a limitation that can lead to a selection bias as those who were aware of ROP and its importance may have chosen to reply to the questionnaire. We cannot say the population of respondents is a representation of these two groups in general and hence the results may not be generalizable to a larger population even though the results are consistent with other studies. The high awareness rates among paramedical staff may be explained by their involvement with the care of preterm babies and ROP and can also be explained by the ROP-specific awareness classes they receive before they are posted for the care of preterm babies. We did not explore each response in detail as part of this questionnaire and hence were unable to explore the possible reasons for the gap in awareness and practice, especially the criteria and timing of screening and modalities of treatment.

CONCLUSION

Our study suggests a high awareness of ROP among the appropriate healthcare practitioners in the study district. However, the suboptimal awareness of management modalities and timing of screening can impact the success of the program and must be addressed urgently.

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Conflicts of interest

There are no conflicts of interest.

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A new technique of phacoemulsification without hydroprocedures

ABSTRACT

Purpose: We describe a new technique where phacoemulsification can be safely performed without doing hydroprocedure. **Materials and Methods:** We conducted a prospective, nonrandomized, noncomparative, single-center study where Group A had undergone phacoemulsification without hydroprocedure and Group B had undergone conventional phacoemulsification. After capsulorhexis, we insert the phacoemulsification tip into the eye without doing any hydroprocedure. First shaving of the cortex and epinucleus is done within the capsulorhexis area. Then, the tip is buried into the center of the nucleus and an anteroposterior crack is fashioned. Then, the tip is placed at 8 o'clock position to chop away a piece of nucleus and emulsified. A similar maneuver is done at 4 o'clock position. The phacoemulsification tip and the chopper are now positioned at the cracked site of the lower fragments. Using the two instruments, the fragments are pushed to the opposite direction and emulsified. **Results:** The mean age of the patients of Group A was 65.7 ± 8.16 years and Group B was 68.9 ± 9.85 years (P = 0.127). The mean best-corrected visual acuity in Group A improved from 0.92 ± 0.49 logarithm of the minimum angle of resolution (logMAR) to 00.01 ± 0.02 logMAR at 3 months postoperatively. The mean endothelial cell loss was 145 ± 123 cells/mm^2 at 3 months postoperatively. There was no significant difference in postoperative outcomes between both the groups. **Conclusion:** The technique can be safely applied in all cataracts, especially posterior polar cataract and white mature cataract where hydrodissection is contraindicated.

Keywords: Chopping, cortical cleavage hydrodissection, hydroprocedure, phacoemulsification

INTRODUCTION

Hydrodissection of the nucleus in cataract surgery has been defined by Faust in 1984 as the injection of fluid into the cortical layer of the lens under the lens capsule to separate the nucleus from the cortex and capsule.[1] The original hydrodissection technique described by Faust was a way to express the nucleus out of the bag in extracapsular cataract extraction (ECCE) surgery. When modern phacoemulsification technique evolved, hydrodissection was more used to facilitate the rotation of the nucleus initially for the divide and conquer technique and later for chopping techniques. Fine described cortical cleaving hydrodissection technique in 1992 where he lifted the anterior capsular flap and injected fluid with a 26G blunt cannula to break the cortical capsular adhesions from the nucleus.[2]

Since its inception, hydrodissection has been an integral part of all types of cataract surgical techniques, namely phacoemulsification, manual small incision cataract surgery, and age-old ECCE. The purpose of doing the hydroprocedure in phacoemulsification is to facilitate easy nuclear rotation and better emulsification.[3] However, the procedure is not always safe as it seems. There have been published reports of posterior capsular rupture (PCR) following hydroprocedure.[4,5] Dislocation of lens nucleus into the vitreous cavity after standard hydrodissection is

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not very uncommon. Intraoperative capsule block syndrome is a well-known complication of hydroprocedure which finally results in PCR and dropping of the nucleus into the vitreous cavity.[6] Hydrodissection cannula-related zonular dialysis is also reported.[7] Phacoemulsification without hydrodissection is a technique which we have developed to prevent hydrodissection-related complications. Two techniques of phacoemulsification without hydroprocedure have been described in the literature. We are describing a new technique, which is very simple, safe, does not need any special maneuvers, reproducible, can be applied in all types of cataracts, and will be especially beneficial in posterior polar cataract or white mature cataract where hydrodissection is better avoided.

MATERIALS AND METHODS

We have been doing phacoemulsification without hydrodissection since 2008 (a film and a paper presented at ASCRS conference at Boston in 2010 and San Diego in 2011, respectively). We conducted a prospective, nonrandomized, noncomparative, single-center, clinical interventional study from January 2019 to December 2019 in a tertiary eye care center of Northeast India. The study protocol was approved by the institutional ethics committee, and it adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all the participants after explaining them study. All patients with age-related cataract requiring phacoemulsification surgery and those who gave informed consent for the study were enrolled. Complete ophthalmic evaluation including medical and ophthalmic history, preoperative uncorrected visual acuity, best-corrected visual acuity (BCVA), the slit-lamp examination to grade the lens and assess the anterior segment, intraocular pressure (IOP) with Goldmann applanation tonometry, and dilated fundus evaluation with indirect ophthalmoscopy was done. Grading of the cataract was done using the Lens Opacities Classification System III (LOCS III).[8] In cases of a dense cataract, B-scan ultrasonography was performed. Biometry was performed with intraocular lens (IOL) Master-500 (Zeiss, Jena, Germany) using partial coherence laser interferometry. In cases of hazy, the axial length was obtained by immersion A-scan and the data were put on IOL Master-500 and the IOL power was calculated. All the enrolled patients were categorized into two groups; in one Group A, phacoemulsification was done without hydroprocedure, while in Group B, conventional phacoemulsification with hydroprocedure was performed.

Surgical technique

All surgeries were performed by a single experienced surgeon (NB) under topical anesthesia (proparacaine 0.5% drops). Two 1-mm side-port incisions were made at 2 o'clock and 9 o'clock position using a microvitreoretinal blade (Alcon Laboratories, Inc.). The irrigating cannula of the bimanual irrigation and aspiration (I/A) apparatus was inserted in continuous irrigation mode to form a stable chamber. A 5.5-mm continuous curvilinear capsulorhexis was performed under irrigation using a 30G cystitome. A temporal limbal incision was made with a 2.2-mm single-bevel keratome (Alcon Laboratories, Inc.). At first, sodium hyaluronate 1.0% (Healon) was injected to form the anterior chamber (AC) and then chondroitin sulfate 4.0%–sodium hyaluronate 3.0% (Viscoat, Alcon Laboratories, Inc.) was injected to coat the endothelium.

All eyes had undergone torsional phacoemulsification (Centurion Vision System, Alcon Laboratories, Inc.) using the active fluidics system with balanced tip. The parameters were set as follows: 60% Ozil, vacuum 400 mmHg, flow rate 30 cc/min, and the IOP being kept at 50 mmHg.

The first step is known as shaving. The bevel of the phaco tip is placed sideways toward the left side instead of the usual bevel-up position. In this step, the cortex and epinucleus within the capsulorhexis boundaries are grasped by the phaco tip and aspirated without using any phaco power [Figure 1a]. In the next step, the phaco tip is buried deep into the center of the nucleus. The nucleus is hold with phacoemulsification probe with adequate vacuum and anterior posterior crack is initiated using chop in situ technique [Figure 1b].[9] In hard, big, and leathery nucleus, a crater is made initially, and then, the chopping is done to crack the nucleus into two halves. Here, step-by-step chopping with lateral separation technique is done to facilitate the crack.[10] After the crack, the phaco tip is placed at 8 o'clock position at the same parameter. The tip holds the nuclear half, slightly lifts it, and pulls little toward the center. Chopping is done at this position to fashion a crack and to take out a triangular piece of the nucleus and subsequently emulsified [Figure 1c]. The tip is now placed at 4 o'clock position to chop and emulsify another triangular piece of the nucleus using a similar technique [Figure 1d]. There remain the last two pieces lying at the incision end. These two pieces were cracked during the first step. Most of the time, they remain adhered loosely. The phaco tip and the chopper are now positioned at the cracked site of these two lower fragments [Figure 1e]. The phaco tip holds the right-hand fragment steady, and the chopper pulls away from the left-hand fragment up toward 6 o'clock position. This fragment is then emulsified. The fourth fragment now lying unattached can quickly be mobilized to 6 o'clock position to complete the emulsification [Figure 1f]. The epinucleus usually comes out along with the nuclear fragment in most of the times. The cortical matter was

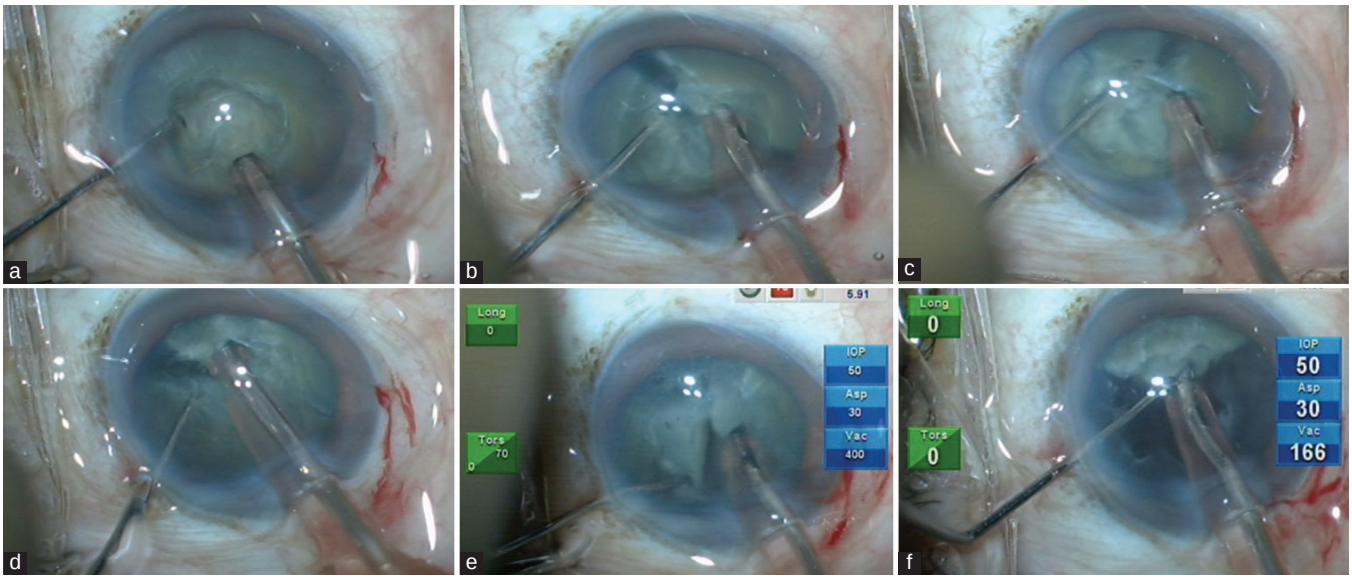


Figure 1: (a) Shaving of the cortex within capsulorhexis margin, (b) Cracking of the nucleus into two halves done, (c) Chopping at 8 o'clock position of the nucleus with removal of a piece of nucleus, (d) Chopping at 4 o'clock position of the nucleus with removal of a triangular piece of the nucleus, (e) The phaco tip and the chopper are now positioned at the cracked site of the lower fragments. Using the two instruments, the fragments are pushed to the opposite direction and are easily taken out one after the other, (f) Last nuclear piece mobilized to 6 o'clock position and emulsified

removed with bimanual I/A. A foldable hydrophobic acrylic single-piece IOL is injected into the capsular bag using the hydroimplantation technique [Figure 2 and Video 1].[11] Intracameral preservative-free moxifloxacin (0.5 ml) was injected into the AC. The main incision and side-port incision were sealed with stromal hydration. The intraoperative parameters such as cumulative dissipated energy, ultrasound time (US time), and fluid loss (ml) was noted at the end of the surgery from the video overlay.

RESULTS

We conducted a prospective, randomized, comparative study to evaluate the outcomes of phacoemulsification without hydrodissection. Table 1 shows the baseline demographics of all the patients. The mean age of the patients of Group A was 65.7 ± 8.16 years and Group B was 68.9 ± 9.85 years. Nucleus hardness was 3.22 ± 0.78 in Group A and 3.55 ± 0.45 in Group B (P = 0.122) (the grading of cataract was done according to the LOCS III). The nucleus was successfully cracked by direct chopping method in majority of the cases. In rest of the cases, a small central crater was made before direct chopping being done. Rotation of the nucleus was attempted in all cases after the emulsification of the second fragment. In most of the cases, the nuclear fragments rotated on the first attempt. In remaining cases, a third chopping was done at 2 O'clock position to fashion another piece of the nucleus. After that, the fragments moved freely to be emulsified as in conventional phaco.

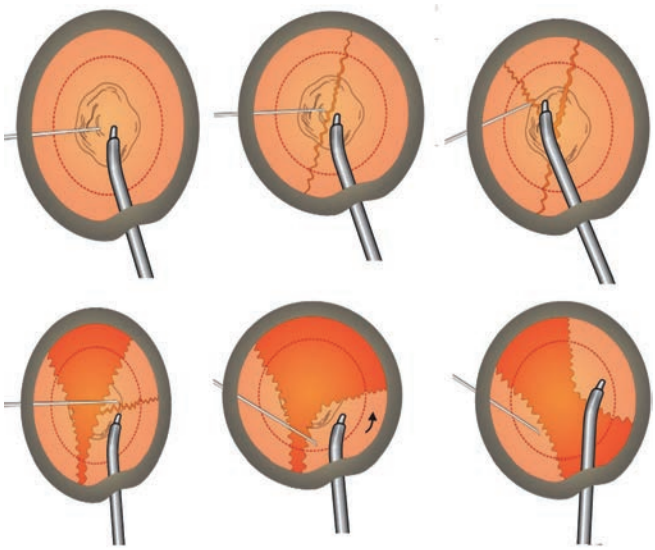


Figure 2: Animated diagrams showing the steps of phacoemulsification without hydroprocedure

Table 2 shows the mean values of intraoperative parameters. In none of the cases, hydrodissection was performed. Nucleus rotation was successful in 100% of cases. PCR was noticed in two cases during last piece removal; we did anterior vitrectomy and implanted the three-piece hydrophobic IOL over sulcus.

Table 3 shows postoperative parameters following phacoemulsification after 3 months. There was no significant difference in BCVA, endothelial cell loss, and IOP between both the groups.

Table 1: Baseline characteristics of the patients

Parameters	Phaco without hydro	Phaco with hydro	*P*
Age (years)	65.7±8.16	68.9±9.85	0.127
Sex (male/female)	0.66±0.34	0.58±0.41	
Laterality (OD/OS)	43/57	52/48	
Cataract grade (LOCS)	3.22±0.78	3.55±0.45	0.122
ACD	3.28±0.32	3.31±0.22	0.641
AL	22.48±0.26	23.54±0.26	0.327
BCVA	0.92±0.49	0.89±0.58	0.971
ECD	2649±250	2439±274	0.199
IOP	13.2±2.34	13.7±1.79	0.459
CCT	522±38.2	526.5±45.3	0.57

LOCS - Lens opalescence classification system, ACD - Anterior chamber depth, AL - Axial length, BCVA - Best-corrected visual acuity, ECD - Endothelial cell density, IOP - Intraocular pressure, CCT - Central corneal thickness, OD - Right Eye, OS - Left Eye

Table 2: Phacoemulsification parameters of the patients

Parameters	Phaco without hydro	Phaco with hydro	*P*
Operation time (min)	10.16±2.54	11.75±2.82	0.019
Total U/S time (s)	52.93±22.16	52.44±15.78	0.571
CDE (units)	13.08±2.84	13.26±1.01	0.168
BSS volume (mL)	45.93±11.34	62.27±3.57	<0.001
Total aspiration time (s)	112.7±21.8	145.6±19.1	<0.001

U/S time - Ultrasound time, CDE - Cumulative dissipative energy, BSS - Balanced salt solution

Table 3: Postoperative parameters after 3 months

Parameters	Phaco without hydro	Phaco with hydro	*P*
BCVA	0.01±0.02	0.01±0.02	0.933
ECD	2414±133	2318±234	0.117
Cell loss	145±123	150±89	0.379
IOP	14.1±2.75	4.5±1.35	0.553
CCT	525±35.9	523±52	0.51

ECD - Endothelial cell density, BCVA - Best-corrected visual acuity, IOP - Intraocular pressure, CCT - Central corneal thickness

DISCUSSION

The significant gain in our technique is that we have been able to avoid the hydroprocedure-related complications such as PCR, capsular block syndrome, and cannula-related zonulolysis. Another benefit of this technique, the epinucleus came out along with the nuclear fragments. This eliminated the need for going to the epinucleus mode. The scanty cortex left at the end of the nucleus removal is another gain. This makes cortex removal and easy and quick.

The primary purpose of doing hydrodissection is to facilitate rotation of the nucleus during phacoemulsification. In our technique, nucleus rotation was not necessary up to Stage 4, i.e. till the 4 o'clock nuclear fragment was not emulsified. After that, the remaining nuclear fragments can be so easily rotated as if somebody has done an excellent cortical cleaving hydrodissection beforehand. Hence, we could have achieved the advantage of nuclear rotation as done in normal hydrodissection without doing so. In our practice, we do not look for corticocapsular adhesion (CCA) in routine preoperative evaluation. Presuming that there were cases of CCA, we operated with the nonhydrodissection procedure; we can say that they did not create any difficulty since we did not have the problem of rotation in any of the cases.

In this technique, we take advantage of a phenomenon called natural hydrodissection.[11] The first step of this phaco procedure, the shaving, allows enough balanced salt solution to pass naturally beneath the anterior capsule to do some hydrodissection. In the second step, when the nucleus is held and lifted little, some more fluid goes around the subcapsular space. In the third step, when the nuclear half is held, lifted, and pulled toward the center at 4 o'clock, one can notice fluid passing through the lateral subcapsular space separating the nuclear epinuclear portion from that of the capsule and cortex. A similar maneuver at the 8 o'clock position separates the other nuclear half free of adhesions. That is why after the removal of the second fragment, the remaining fragments become adhesion free and can easily be rotated. In manual hydrodissection, there may be an error in finding the right path of the fluid. In natural hydrodissection, the fluid finds its path naturally, thus eliminating any error.

Masuda and Tsuneoka described a technique of hydrodissection-free phacoemulsification in which they apply mechanical sweeping movements to break the CCAs.[12] This technique of mechanical sweeping may cause stress on the zonules and cause zonular dialysis. Hence, is it not a suitable technique in cases of zonular weakness, subluxated cataract?

In semi-crater and split technique by Soda and Yaguchi, a wall is sculpted perpendicular to the center of the nucleus and the nucleus is split into two sections. In the next step, multiple pie-shaped sections or L-shaped fractures are created, facilitating rotation and removal of the nuclear pieces.[13] In this technique, the authors themselves have admitted that this technique is not suitable for hard, brown cataracts.

Compared to these two techniques, our technique can be applied safely in all types of cataracts including cataracts with weak zonules and any type of hard, brown and even in leathery cataracts. Our technique hardly differs from the conventional phacoemulsification technique, except that the chopping at 4 o'clock and 8 o'clock is little unconventional as most of the phaco surgeons like to do chopping in the area around 6 o'clock.

In our study, we have performed this technique in cases with pseudoexfoliation syndrome, posterior polar cataract, brunescent, white cataract, small pupil, shallow AC, long axial length, postvitrectomy, and intraoperative floppy iris, which are categorized as high-risk cases.[14]

In respect to the teaching point of view, in our hospital, all our resident surgeons are encouraged to perform the hydrodissection-free phacoemulsification. Initially, we teach them to divide and conquer technique[15] for initial few days, but once they got the hangover of phacoemulsification, then we shift them to hydrodissection-free phacoemulsification and they have been performing with favorable outcomes. We have not included their performed cases in the study, but a comparative study between an experienced surgeon and a resident surgeon will be very beneficial.

CONCLUSION

Vigorous hydrodissection can cause many complications such as PCR, nucleus drop, and zonular dialysis. Two techniques of phacoemulsification have been described in the literature to overcome this problem.[12,13] This nonhydroprocedure technique of phacoemulsification holds good in the 1442 cases that we have operated at our hospital. The experience of these cases makes us believe that this technique can be easily apply to overcome those problems and can be a major technique in posterior polar cataract where hydroprocedure is contraindicated.

Declaration of the patient consent

Informed consent was obtained from all individual participants included in the study. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The participants understand that their names and initials will not be published and due efforts will be made to conceal their identity.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Bilateral vitreous hemorrhage with branch retinal vein occlusion secondary to hyperhomocysteinemia: A rare case report

ABSTRACT

Retinal vascular occlusions are uncommon in young people and require more in-depth investigation into the cause. A high level of circulating homocysteine carries a risk for retinal vaso-occlusive events. We, hereby, report a rare case of hyperhomocysteinemia-related bilateral branch retinal vein occlusion (BRVO). A 27-year-old male presented with sudden painless gross diminution of vision in the left eye (LE) for 10 days. Further assessment revealed inferotemporal BRVO (ITBRVO) in the right eye (RE) with mild vitreous hemorrhage (VH) and dense VH in the LE. Extensive investigations into the cause revealed an elevated level of serum homocysteine. The patient was started on Vitamin B6 and B12 supplementation. RE sectoral panretinal photocoagulation and LE pars plana vitrectomy were done. LE ITBRVO was noted intraoperatively for which endolaser was done. Hyperhomocysteinemia through its prothrombotic properties is an independent modifiable risk factor for vascular thrombotic events. Hence, it should be considered as a differential diagnosis for retinal vascular occlusions to prevent further recurrences and cerebrovascular events, especially in young adults.

Keywords: Bilateral branch retinal vein occlusion, hyperhomocysteinemia, vitreous hemorrhage

INTRODUCTION

Bilateral retinal vein occlusions (RVO) are very rare with a 0.04% of 15-year cumulative incidence as reported in Beaver Dam study.[1] Bilateral RVO in young adults may be the initial presentation of a severe potentially life-threatening systemic disease. It, therefore, warrants detailed systemic workup to rule out hypercoagulable, myeloproliferative, and inflammatory disorders. Hyperhomocysteinemia is one such common hypercoagulable state causing vaso-occlusive events. Only very few cases of branch retinal vein occlusion (BRVO) secondary to hyperhomocysteinemia have been reported in literature.[2-4] We, hereby, report a unique case of bilateral inferotemporal branch retinal vein occlusion (ITBRVO) associated with dense visually debilitating vitreous hemorrhage (VH) in one eye and mild inferior VH in the other eye in a young healthy male with hyperhomocysteinemia.

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CASE REPORT

A 27-year-old male presented to us with a history of sudden-onset painless gross diminution of vision in the left eye (LE) for 10 days associated with floaters. There was no history of trauma to the eye and no similar history in the past. There were no visual complaints in his right eye (RE). He had no other systemic comorbidities. He was a nonsmoker. On examination, best-corrected visual acuity (BCVA) was 6/6 in the RE and hand movements in

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the LE. Anterior segment examination was normal in both the eyes. Fundus examination of the RE showed multiple superficial retinal hemorrhages with sclerosed vessels in the IT quadrant suggestive of ITBRVO [Figure 1a and b]. There was also mild dispersed VH inferiorly. Media was very hazy in the LE due to dense dispersed VH with no view of the retina. Ultrasonography-B scan of the LE confirmed the presence of VH with total posterior vitreous detachment and no evidence of retinal detachment [Figure 2a]. Complete hemogram, blood sugar profile, erythrocyte sedimentation rate, and renal function test were all within the normal limits. C-reactive protein and Mantoux tests were negative. Chest X-ray was normal. Workup for systemic vasculitis including antinuclear antibody and antineutrophil cytoplasmic antibodies was normal. Protein C, Protein S, and antithrombin III levels were normal. Serum homocysteine level was, however, found to be elevated,- 30.12 µmol/L. The patient was started on capsule homocheck (cyanocobalamin 400 µg + pyridoxine 10 mg + folic acid 1 mg) and tablet Vitamin C 500 mg BD. RE sectoral panretinal photocoagulation was done in the IT quadrant. One month later, RE fundus examination showed resolved vitreous and retinal hemorrhages, whereas LE showed nonresolving VH. BCVA in the RE was 6/6 and hand movements in the LE. Pars plana vitrectomy was done subsequently in the LE. Intraoperative fundus examination in the LE showed superficial retinal hemorrhages, new vessels, and sclerosed vessels along the IT quadrant suggestive of LE ITBRVO [Figure 2b]. Endolaser was done along the IT quadrant during vitrectomy. BCVA in the LE improved to 6/6 2 weeks following surgery. Both eyes maintained *status quo* at 12 months of follow-up till date.

DISCUSSION

VH is one of the most important causes for spontaneous and sudden-onset gross diminution of vision in an young adult. Spontaneous VH in young adults can be secondary to high-risk proliferative diabetic retinopathy (PDR), ischemic RVO, familial exudative vitreoretinopathy, hematological disorders and blood dyscrasias including proliferative sickle-cell retinopathy and leukemias, and retinal vasculitis including Eales disease, tuberculosis (TB), and systemic lupus erythematosus (SLE). Blood sugar profile, blood pressure, and complete hemogram including peripheral smear evaluation were all normal in our case, thereby ruling out PDR and hematological disorders. Eales' disease is another common differential diagnosis for VH in the young healthy Indians. More than 60% of cases have vitreous hemorrhage at presentation.[5,6] Chest X-ray and Mantoux test were normal in our case, thereby ruling out TB and Eales' disease. Another important etiology of VH to consider in our case was RVO. The RE had shown BRVO with retinal hemorrhages and mild VH (occlusive vasculopathy) at presentation, whereas the LE also had evidence of occlusive vasculopathy based on intraoperative retinal examination. Therefore, we had a provisional diagnosis of bilateral RVO or occlusive vasculopathy with VH in our case. Bilateral RVOs are very rare as reported in Beaver Dam study.[1] Bilateral RVO warrants more extensive evaluation to rule out all possible systemic diseases – diabetes, elevated blood pressure, hypercholesterolemia, hypercoagulable, myeloproliferative and inflammatory disorders, etc., Hypercoagulable disorders causing retinal vascular occlusive disease include hyperhomocysteinemia, antiphospholipid syndrome, factor V Leiden mutation, protein C and S resistance, and antithrombin deficiency. Myeloproliferative disorders comprise of polycythemia, multiple myeloma, Waldenström macroglobulinemia, etc., whereas inflammatory conditions include occlusive periphlebitis-sarcoidosis, SLE, and Behçet's disease.[7] Systemic workup for all suspected etiologies for bilateral RVO in our case was normal except for elevated serum homocysteine level. Various studies have shown relations of elevated serum levels of homocysteine with occurrence of RVOs, but there is a lack of conclusive evidence for this association.[8,9] Carral-Santander *et al*. have

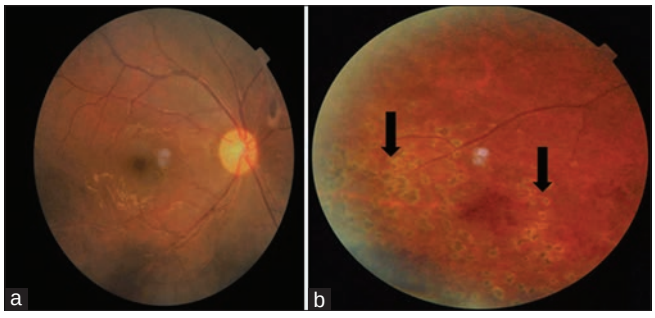


Figure 1: Fundus images of the right eye (a and b) showing retinal hemorrhages in inferotemporal quadrant, sectoral laser marks (arrows), and mild vitreous hemorrhage suggestive of inferotemporal branch retinal vein occlusion

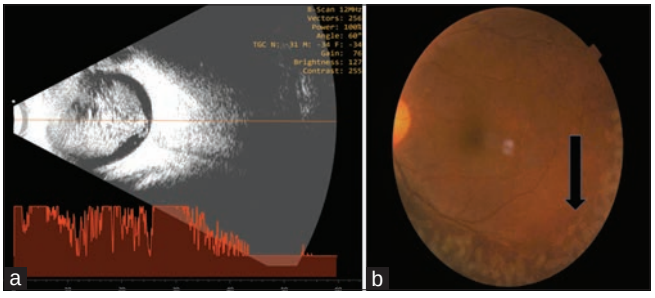


Figure 2: Ultrasound B scan image of the left eye (a) showing dense vitreous hemorrhage and total posterior vitreous detachment, and fundus image of the left eye in the postoperative period (b) showing sclerosed vessel (arrow) in the inferotemporal quadrant and endolaser marks suggestive of inferotemporal branch retinal vein occlusion

reported a case of bilateral retinal occlusive vasculopathy involving both retinal arteries and veins in a 43-year-old male secondary to hyperhomocysteinemia.[3] Gore *et al*. have reported unilateral extramacular multiple BRVOs in a 45-year-old male with hyperhomocysteinemia.[2] Kumar *et al*. have reported unilateral central retinal vein occlusion with cilioretinal artery occlusion in a 27-year-old healthy male with hyperhomocysteinemia.[4] To the best of our knowledge, ours is the only case report with bilateral VH secondary to extramacular BRVO in a case of hyperhomocysteinemia.

Hyperhomocysteinemia is one of the most common causes of hypercoagulable disorder. It can be graded as mild (15–30 μmol/L), moderate (30–100 μmol/L), and severe (>100 μmol/L) based on fasting serum concentrations. Mild-to-moderate elevation of plasma homocysteine levels is usually associated with retinal vascular occlusive disease. Our patient also had moderately elevated (30.12 μmol/L) serum homocysteine levels. Hyperhomocysteinemia-related retinal blood vessel damage is multifactorial and includes induced oxidative stress (redox stress), reduced nitric oxide bioavailability, altered expression of various thrombotic factors, increased platelet activation, increased coagulability, and mutagenic effect on the arterial smooth muscle cells.[2,9,10]

Treatment of the RE in our case included sectoral laser of IT quadrant. Treatment of the LE included pars plana vitrectomy with endolaser. Frequent follow-up is advised in such cases to check for the adequacy of treatment and also to detect any new episodes of vascular occlusion as they are prone to bilateral and multiple vascular occlusions. It is also essential to detect and treat any underlying cause of secondary hyperhomocysteinemia. Vitamins B6 and B12 and folic acid are important cofactors necessary for transsulfuration and re-methylation of homocysteine. Oral supplementation of these cofactors is, therefore, recommended to improve homocysteine metabolism and potentially reduce the incidence of future vascular occlusive events as well as improve vascular endothelial functions.[3]

CONCLUSION

Hyperhomocysteinemia should be considered as a differential diagnosis for retinal vascular occlusions with or without VH in young adults. Patients presenting with such a clinical picture should undergo thorough investigations to identify and treat any modifiable risk factor such as hyperhomocysteinemia. This will ensure the prevention of any further fatal thromboembolic or vaso-occlusive events in the future.[2,6]

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.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Solitary eccrine spiradenoma of caruncle: A rare occurrence

ABSTRACT

Eccrine spiradenoma (ES), a sweat gland tumor, is rarely found in the caruncle. Although the occurrence of spiradenoma of carbuncle are rare. On account of the histological composition of the caruncle, which includes, in addition to conjunctiva, hair follicles, sebaceous glands, sweat glands, and accessory lacrimal tissue, the caruncle may develop lesions that may be similar to those found in the skin, conjunctiva, or lacrimal gland. We encountered a 39-year-old female with a nodular growth in her left caruncle, which had developed over the last 10 years. Excision biopsy was carried out under local anesthesia. The histopathology was suggestive for a benign ES. Clinical preoperative diagnosis is very difficult for caruncular lesions and is reached only in about half of the cases. Most lesions of the caruncle are benign, mainly nevi. Reported malignant lesions are very rare, but can be potentially fatal. The possibility of sweat gland tumor should be kept in mind in the diagnosis of caruncle tumors.

Keywords: Caruncle, eccrine spiradenoma, solitary mass

INTRODUCTION

The caruncle (from Latin caro = flesh) is a soft, pink, ovoid body, about 5 mm high and 3 mm broad, situated in the lacus lacrimalis medial to the plica semilunaris. It is more prominent on lateral gaze and is retracted on medial gaze.

The eccrine spiradenoma (ES) is a benign neoplasm of the skin first described by Kersting and Helwig, who considered it to be a derivative of eccrine sweat glands. It usually presents as a solitary, intradermal, and painful nodule, the most common sites being the chest and face.[1]

ESs are benign tumors of the skin found at the site of eccrine sweat glands.[2]

To the best of our knowledge, there has been no report of a primary spiradenoma developing in the palpebral conjunctiva involving caruncle.[3]

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CASE REPORT

A 39-year-old female presented in November 2019 with a nodule in the left caruncle for the last 2 years, which had been gradually increasing in size and painless. The swelling measured 3 mm × 2 mm × 1.2 mm and pink in color with no overlying vascularity [Figure 1].

The growth was firm in consistency and nontender to touch and was negative on translucency test. The surrounding skin and eyelid margin were normal. An ophthalmic examination revealed nothing abnormal, and the patient's vision was 6/6 in both the eyes. A general physical examination also showed nothing abnormal. There was no enlargement of auricular,

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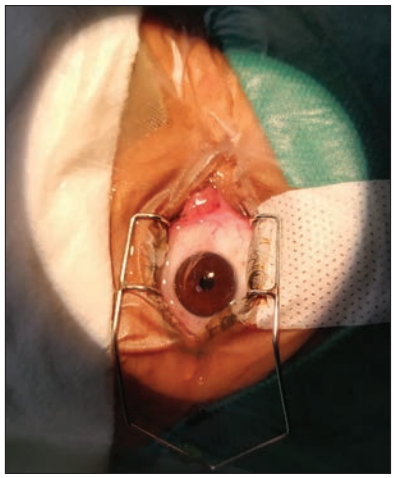


Figure 1: Intraoperative image of caruncle mass

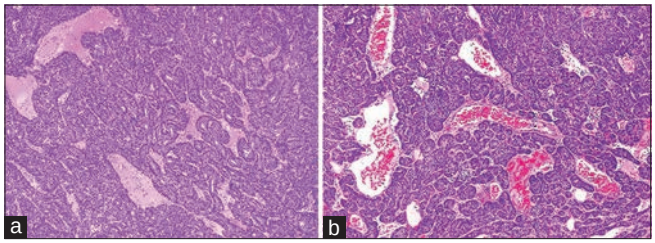


Figure 2: (a) H and E stained section showed keratinized stratified squamous epithelium with tumor mass in nest and lobules. (b) H and E-stained section showing tumor cells are basaloid with scanty cytoplasm, mild pleomorphism, present with peripheral palisading



Figure 3: Postoperative clinical photo after excision of caruncle mass

cervical, or submandibular lymph nodes; the general systemic examination was normal. Clinically, the cystic lesion of the caruncle was suspected, and a full-thickness wide excision of the mass was carried out.

Laboratory data including blood chemistry and serum level of tumor markers were within the normal range. No abnormal findings were seen in the chest X-rays.

Intraoperative findings: Shave excision of the mass was carried out, and the mass was soft to firm in consistency, noncapsulated, and not extending to the surrounding tissue. Bleeding was minimal as the mass was relatively avascular. Care when dissection was taken not to go deep to injure the medial longitudinal ligament and avoided making an opening in the conjunctiva.

Histopathology report

Gross appearance-received soft tissue measuring 2.5mmx2mmx1.5mm.

External surface gray white congested was gray-white, firm, and had a rubbery surface.

As shown in Figure 2a Microscopic examination showed keratinized stratified squamous epithelium with underlying dermis showing a tumor mass in the nest and lobules.

Tumor cells were basaloid with scanty cytoplasm, And mild pleomorphism, present with peripheral palisading and clefting within the nest of some cells arranged in glandular pattern along with lymphocystic infiltrate Figure 2b.

Post-operative day 2 clinical picture of patient [Figure 3]. A spiradenoma is a type of sweat gland tumor, which has a comparatively good clinical course.

DISCUSSION

ES, first described in 1956, is an uncommon, benign, dermal tumor of apocrine differentiation derived from cutaneous sweat glands.[4] It usually presents as a solitary, intradermal, and painful nodule, the most common sites being the chest and face.

A spiradenoma is a tumor of the eccrine sweat glands that arises as a solitary, intradermal, and painful nodule on the chest or face and most frequently in early adulthood. Occasionally, there may be multiple tumors.[1]

It has been well characterized in the dermatological literature, but not in the ophthalmological literature, probably because it is uncommon in the eyelid and caruncle [Table 1].[5,3]

In our case, the tumor was a solitary lesion at caruncle (site in the palpebral conjunctiva of the eyelid). The majority of spiradenomas have a benign course,[3] and local recurrences have not been reported. Mochizuki *et al*. reported a lesion of local recurrence because of an inadequate surgical removal, treated the site of the tumor excision with adjunctive cryotherapy to prevent further recurrences.[6]

Malignant changing of spiradenomas is unusual, and the histology of malignant spiradenomas resembles squamous

Table 1: Cases reported

Author	Age/gender	Location	Size (mm)
Ahluwalia *et al.*	55/female	Left upper eyelid	24×20×12
Amann *et al*.	60/female	Right upper eyelid	10×8
Gupta *et al*. (India)	23/female	Left eyelid	-
Singh *et al*. (India)	73/male	Left upper eyelid	11×9

metaplasia or very poorly differentiated pseudosarcomatous spindle cell elements.[4]

In cases of a malignant transformation, the patient might die of systemic metastases several months after the diagnosis.[4]

ESs are benign tumors of the skin found at the site of eccrine sweat glands.[2] It belongs to the group of the painful tumors of the skin, also known as the acronym BLEND AN EGG. This group includes blue rubber bleb nevus, leiomyoma, ES, neuroma, dermatofibroma, angiolipoma, neurilemmoma, endometrioma, glomangioma, and granular cell tumor.[1,2]

In contrast, the pain arising from an adenoid cystic carcinoma due to infiltrative growth and perineural invasion, however; the pain in ES is related to the presence of small unmyelinated axons in connective tissue around the tumor, or Due to the expansion of the cysts.

ES can cytologically simulate an adenoid cystic carcinoma on fine-needle aspiration cytology because both tumors contain hyaline globules.

Histologically, the tumor is lobular, with two types of cells in the islands. Larger, paler cells are grouped around lumina and smaller, darker cells form the periphery.[7-9] Of the lobule.

Malignant degeneration of spiradenoma usually appears in long-standing tumors and is clinically revealed by a rapidly enlarging tumor mass.[2,10] In these cases, the diagnosis of spiradenocarcinoma is made only if a residual benign component is identified.

Clinical differential diagnosis-Caruncle granuloma, caruncular cyst, caruncular hypertrophy.

Histological differential diagnosis

A primary basal cell epithelioma with eccrine differentiation and a lobular, hyalinized syringoma (cylindroma) are conditions which are a prerequisite for the histological differential diagnosis of ES.

A basal cell epithelioma displays a margin of basal cells with a neat, radial configuration.[2] It recapitulates the inferior layer of normal epidermis with vertically articulated basal cells.

A cylindroma is characterized by prominent, hyalinized bands of collagen enveloping and intertwining amidst the tumor lobules and cellular constituents.[2,10]

ES enunciates compressed tumor lobules of varying dimensions with sharp basophilia. Lightly stained and adjunctive compact, intensely stained, peripheral nuclei are distinctly discernible.[6,2]

CONCLUSION

A spiradenoma is a type of sweat gland tumor, which has a comparatively good clinically course, but malignant transformation after repeated recurrences should be speculated.

Surgical excision remains the therapeutic option of choice with minimal incidence of reoccurrences.

Any change in color, size, or vascularization of a caruncular lesion should be excised. Pathological examination should be mandatory.

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.

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Conflicts of interest

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Case Report

A descriptive presentation of a family showing various features of aniridia and its genetic analysis

ABSTRACT

The abnormal neuroectodermal development due to the PAX 6 gene mutation results in aniridia, a rare disorder. We report herein a family that presented with aniridia, myopia, ptosis, glaucoma, cataract, and sensory nystagmus. This family provides a unique resource for the mutational analysis of the CRYBB1, CRYBA4, and PAX-6 gene. In addition, it is important to remember that mutations are often a part of these ocular abnormalities. Patient awareness, education, and involvement in treatment are essential to prevent amblyopia associated with the cataract and nystagmus related to aniridia.

Keywords: Aniridia, cataract, Wilms tumor

INTRODUCTION

Congenital aniridia is a rare ophthalmic condition (incidence between 1:64,000 and 1:100,000) that generally affects both eyes (OU).[1] The name is derived from iris hypoplasia, the most evident manifestation, which can range from almost total to only a mild phenotype. Other manifestations include nystagmus, dry eye and keratopathy, glaucoma, lens opacities, and subluxation, along with retinal, macular and optic nerve disorders, strabismus, and poor visual acuity (VA).[1] Since visual prognosis in patients with aniridia remains poor, the understanding of its genetic basis is critical toward preparing the ground for targeted future treatment options based on specific mutations.[2,3]

CASE REPORT

A 12-year-old boy (child 1) presented to our outpatient department with decreased vision and involuntary movements of OU since birth. There was no history of photophobia, trauma, prolonged drug intake, or any other systemic abnormalities. He was born at term, with no history of consanguinity. His mother and two older male siblings had similar complaints. His father and younger sister were apparently unaffected.

VA OU was 20/200, improving to 20/80 with pinhole. Ocular examination revealed bilateral mild-to-moderate ptosis, along with pendular nystagmus. Intraocular pressure (IOP) as recorded with Goldman Applanation Tonometer was 20 mm of Hg in the right eye (OD) and 18 mm of Hg in the left eye (OS). Anterior segment examination showed transparent corneas with normal sensations and bilateral complete aniridia [Figure 1]. Both lenses were seen to be subluxated superiorly with posterior polar cataracts with spokes. Fundus examination of OU revealed a C: D ratio 0.3:1 and 0.4:1 for the right and OS, respectively. He was advised antiglare glasses after refraction, and his best-corrected VA was 20/80 in OU with −3DS in right eye and −4DS in left eye.

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Examination of the family

His 16-year-old sibling (child 2) had a VA of 20/200 OU, with no improvement with pinhole. The IOP was 28 mm of Hg and 36 mm Hg, respectively, with associated nystagmus. He had bilateral aniridia with bilateral posterior polar cataracts with the superiorly subluxated lens. The fundus examination revealed optic disc cupping of 0.6 OD and 0.8 OS, respectively. The child was started on Latanoprost eye drop at night time and advised combined trabeculectomy with lens extraction OS, followed by OD. He underwent trabeculectomy OS during the postoperative period; his IOP was 18 mm Hg in the operated eye. Without any antiglaucoma medication, bleb is well-formed, vascular, and 20 mmHg OD.

His other 14-year-old sibling (child 3), had a VA of finger counting at 2 m OU. The IOP was 22 mm of Hg and 20 mm Hg, respectively, with associated nystagmus. Anterior segment examination revealed bilateral aniridia with bilateral posterior polar cataracts, as in the index case. The fundus examination of OU revealed no abnormalities. He was also advised antiglare glasses after refraction, and his best-corrected VA was 20/120 in OU with −4.5DS in OU.

Examination of mother

The VA was OD 20/200, and OS finger counting at 3 meters. IOP in OU was 18 mm Hg. Anterior segment examination revealed bilateral aniridia with bilateral posterior polar cataracts, with no nystagmus. The fundus examination was unremarkable. Bilateral cataract surgeries with IOL implantation were planned, under guarded visual prognosis, for her, but she refused. None of them had any significant systemic abnormalities.

On genetic analysis, direct sequencing of the coding region and of the flanking intronic sequences of CRYBB1, CRYBA4, and PAX6 genes revealed four nucleotide variations [Table 1 and Figures 2,3].

All the detected variations have been reported in the literature. The CRYBB1 (rs57400078) nucleotide change was found in three members of the family, whereas the other two did not harbor the same change. Two polymorphisms were detected in the CRYBA4 gene (rs5761637 and rs4276) in all the family members. PAX6 sequencing revealed one synonymous nucleotide variation (c. 764A > G) present in all the affected members of the family. Nucleotide change detected in the CRYBB1 and CRYBA4 genes were found to be nonpathogenic in silicon analysis [Table 2]. Of the total four variations observed, only a single missense mutation in the PAX6 gene (c. 764A > G or p.Gln255Arg) was identified. This nucleotide variation lies in the last codon of exon 9 in the highly conserved homeodomain and leads to change at amino acid position 255 from glutamine to arginine.

The main differential diagnosis was WAGR syndrome this is an entity that is characterized by the presence of Wilms' tumor, aniridia, genitourinary anomalies, and mental

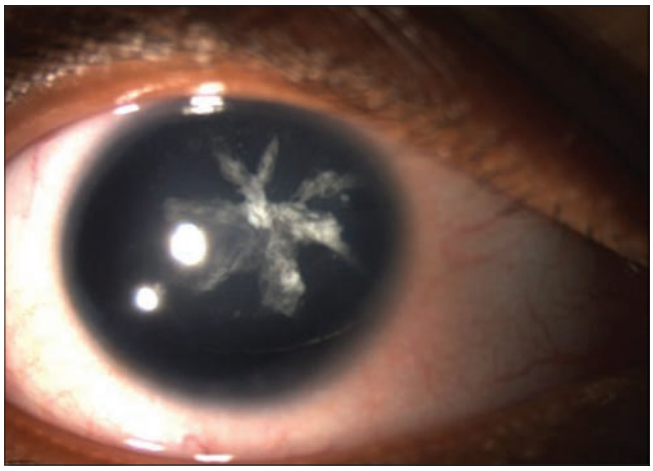


Figure 1: Aniridia with superiorly subluxated lens with congenital posterior polar cataract with spokes in the index case

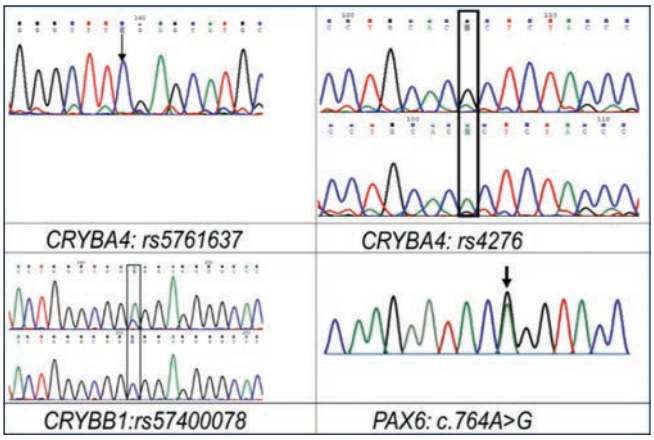


Figure 2: Genetic analysis of the PAX 6 gene, showing a positive correlation

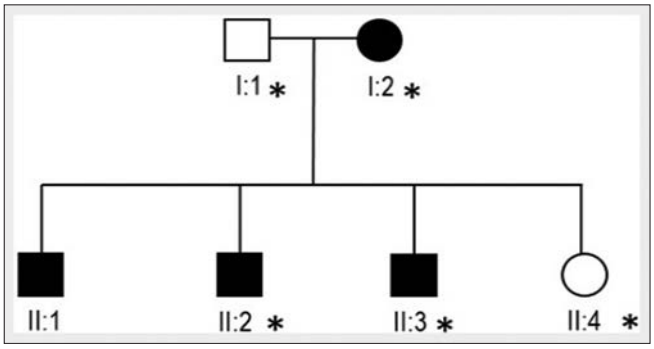


Figure 3: Pedigree of aniridia affected family. In the pedigree, the square symbol represents males while the circle symbol represents females. Blackened symbol denotes an affected individual. The asterisks indicate the individuals whose DNA samples were available for genetic analysis

Table 1: All nucleotide variations found in *CRYBB1, CRYBA4* and *PAX6* genes

Patient ID	*CRYBB1*	*CRYBA4*	*PAX6*
I:1	Nil	rs5761637, rs4276	Nil
I:2	rs57400078	rs5761637, rs4276	c.764A>G
II:1	rs57400078	rs5761637, rs4276	c.764A>G
II:2	rs57400078	rs5761637, rs4276	c.764A>G
II:3	Nil	rs5761637, rs4276	c.764A>G

Table 2: Schematic diagram of *CRYGC* gene showing the site of nucleotide change

Nucleotide variation	HMF analysis
CRYBB1:rs57400078	No splicing error
CRYBA4:rs5761637	No splicing error
CRYBA4:rs4276	No splicing error
PAX6:c.764A>G	Splicing error

HMF – Hydroxymethylfurfural

retardation. In our patients, the IQ level and abdominal ultrasound were normal, so WAGR syndrome was ruled out. Another differential diagnosis was Gillespie's syndrome that is characterized by cerebellar ataxia and mental retardation. We ruled out this by getting a neurological and psychiatric examination, which stated that gait and IQ were normal, respectively.

DISCUSSION

Aniridia is a complex neuroectodermal developmental disorder characterized by a variable degree of hypoplasia or the absence of iris tissue, associated with multiple other ocular changes, presenting from birth or progressively over time. Pan ocular changes occur as a result of a mutation in the PAX6 gene, which is a developmental ocular gene. These changes include alterations in corneal cytokeratin expression, cell adhesion, and stem cell deficiency. It also has a fibrotic nature, which may fail filtration surgery. However, there are few reported cases with no identified mutation of PAX6.[4,5]

Classic aniridia presents a Mendelian inheritance pattern and is an autosomal dominant disease, due to loss of function of one of the copies of the PAX6 gene. It is detectable in 90% of the cases, resulting from genetic mutations in 2/3 and from chromosomal rearrangements in 1/3).[5,6] It codifies a regulator protein essential for the genesis of the cornea, iris, lens, drainage angle of the eye, ciliary body, and all the retinal layers. Three phenotypes have been described Autosomal dominant accounting for about 85% of cases and not associated with other systemic anomalies. Congenital sporadic seen in 13% of all aniridia and occurs in association with WAGR (Wilms' tumor, aniridia, genitourinary anomalies, and mental retardation) syndrome. Less than 2% are autosomal recessive, often associated with Gillespie's syndrome (cerebellar ataxia and mental retardation).[2,4]

Most cases present within 6 weeks of birth, with an obvious iris abnormality or nystagmus. Affected individuals characteristically have absent or altered iris tissue and foveal hypoplasia, leading to nystagmus and impaired VA. Progressive visual failure occurs due to late-onset cataracts, glaucoma, and corneal opacification.

There is no direct correlation between genotype and phenotype, with many clinical variations. Moreover, there is also phenotypic variability between affected members of the same family. This case series highlights that PAX 6 mutations are common in aniridia. This case highlights that in case of association of aniridia with cataract or glaucoma, timely management is very important to prevent visual impairment due to amblyopia. A proper coordination between ophthalmologist and pediatrician plays an important role for the detailed ophthalmic evaluation of all family members in all cases of aniridia along with a proper systemic evaluation to rule out other associated syndromes, for example, WAGR and Gillespie syndrome in these familial aniridia cases. Furthermore, greater awareness regarding various manifestations based on severity is required as subtle variants of the disorder are often missed/misdiagnosed. Genetic testing has a very important role in confirming the investigation of PAX 6 mutation and determine if an individual is at a risk of Wilms' tumor.

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.

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Case Report

Challenges in the diagnosis of early endogenous fungal endophthalmitis

ABSTRACT

Endogenous fungal endophthalmitis (EFE) is an uncommon disease caused by the dissemination of fungal infection to posterior segments of the eye and has a high rate of visual loss. Most patients have associated predisposing risk factors, including immunocompromised conditions, and the condition is less likely to occur in healthy individuals. Here, we report two patients who presented like uveitis and deteriorated after starting standard treatment for uveitis, which included steroids. They were later diagnosed with EFE. Fungal endophthalmitis should be suspected even in ambulatory individuals with immunocompromised states, when they present with uveitis like features, before starting steroid treatment. Polymerase chain reaction based diagnosis is extremely useful and should be considered in diagnosing EFE.

Keywords: Endogenous fungal endophthalmitis, molecular diagnosis, uveitis

INTRODUCTION

The morbidity and mortality rates associated with fungal infections are high, and prevention, diagnosis, and treatment of these infections remain a challenge. Most of the fungal pathogens are opportunistic, and infection becomes invasive only when predisposing factors such as immune deficiency or other underlying severe disease are concomitantly present.[1] Endogenous fungal endophthalmitis (EFE) is most commonly caused by *Candida albicans*, followed by *Aspergillus species*, and have a high chance of visual loss and poor visual outcome.[1]

Candida is a commensal but can cause problems when body's defense mechanisms are abridged or when patients undergo certain procedures, such as bladder catheterization or urologic surgery, which increases colonization of mucosal surfaces. The biofilm formation gives protection to the organism from host defense and in developing antifungal drug resistance.[2] *Aspergillus* species are filamentous fungi commonly found in the natural environment, but when the patient's immunity is weak, the inhaled spores can reach the bloodstream. Through blood, these microbes can get dispersed to other organs,[3] including eye, causing infection.

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We report herein two cases of unilateral EFE; first case: *candida tropicalis* and second case: *aspergillus* species presented as uveitis in patients with predisposing factors but were otherwise ambulatory and came as outpatients in a standalone tertiary eye hospital. Treatment with systemic steroids worsened the condition, and traditional microbial culture was negative for fungal infection. This report emphasizes the need for encouraging molecular diagnostics in patients having predisposing factors, and not to solely rely on less sensitive traditional diagnostics.[4]

CASE REPORT

Case 1

A 62-year-old male came to our eye hospital with pain, redness, photophobia for 5 days, and decreased vision for 2 days in the left eye. He had a history of portal hypertension

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and liver cirrhosis and a known diabetic under control. His history was significant for recent hospitalization for urinary tract infection. On examination, the patient's best-corrected visual acuity was 6/6, N6 in the right eye, and 6/12, N8 in the left eye. His left eye was congested, pseudophakic with anterior chamber inflammation with anterior vitreous cells. Fundus view was hazy but within the normal limits barring a few exudates in the inferior anterior vitreous. The fellow eye was completely normal. Diagnosed with intermediate uveitis with anterior spillover, he was treated with topical 1% prednisolone acetate and cycloplegics. Diagnostic workup for uveitis did not reveal any infection or immune-mediated etiology. Hence, he was started on systemic steroids after physician's clearance. However, his vision rapidly dropped to hand movements with the development of hypopyon [Figure 1] and coarse vitreous opacities. B scan ultrasonography showed thickened choroid with hyperechoic vitreous echoes [Figure 2]. A vitreous sample was sent for culture and polymerase chain reaction (PCR) and were positive for *Candida tropicalis*. Urine culture revealed *Candida* species, while blood culture was negative. He was treated with intravitreal voriconazole (0.1 mg/0.1 ml), topical 1% voriconazole, and systemic fluconazole 400 mg per day, with no improvement. Core vitrectomy was then performed with intravitreal voriconazole. Systemic fluconazole was continued for 6 weeks, which helped to resolve the infection completely, with no visual improvement.

Case 2

A 53-year-old male complained of severe pain and loss of vision in his right eye for one month. He was treated as uveitis with topical prednisolone acetate and systemic steroids elsewhere with no improvement and gradual worsening. He had a history of recently detected carcinoma prostate with vertebral metastasis, for which chemotherapy had been deferred because of ocular problems. On examination, his visual acuity was no perception of light in the right eye and 6/6, N6 in the left eye. The eye had a severe fibrinous reaction in the anterior chamber with hypopyon and no view of the fundus. B-scan ultrasonography showed pronounced vitreous opacities and choroidal thickening [Figure 3]. Lensectomy with vitrectomy was performed. The vitreous sample sent for diagnostic microbiology showed fungal hyphae in gram stain and KOH [Figure 4], but the vitreous culture was negative. PCR revealed *aspergillus species*. The patient was treated with topical, systemic, and intravitreal voriconazole. However, due to persisting pain and insignificant clinical improvement, evisceration was performed and sent for histopathology, which showed fungal granuloma with inflammatory cells.

DISCUSSION

Endophthalmitis is one of the most devastating eye infections and may lead to irreversible blindness in the infected eye within hours or days of symptom onset. The risk factors for EFE include systemic diseases such as diabetes, liver cirrhosis, malignancy, acquired immunodeficiency syndrome, and immunocompromised states.[5] Among all cases of EFE, endogenous *C. albicans* endophthalmitis is the most common causative organism, representing 75%–80% of the cases, followed closely by *Aspergillus* species.[6] Classically EFE is suspected in patients who are either febrile or hospitalized. The presentation is commonly bilateral, can be asymmetric, although unilateral cases have been reported.

The patients reported here had risk factors of liver cirrhosis, diabetes mellitus, or malignancy, but they were otherwise ambulatory and were seen as outpatients in a standalone tertiary eye hospital. The examination did not show typical EFE features like posterior pole chorioretinitis lesions.[7] They were treated as idiopathic intermediate

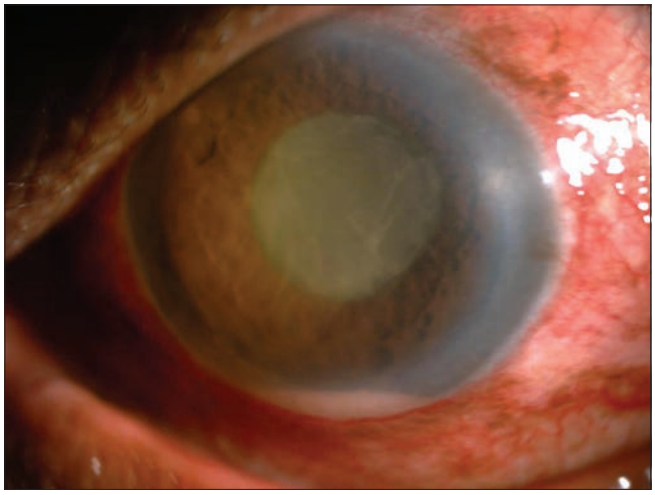


Figure 1: Pseudophakic left eye showing hypopyon

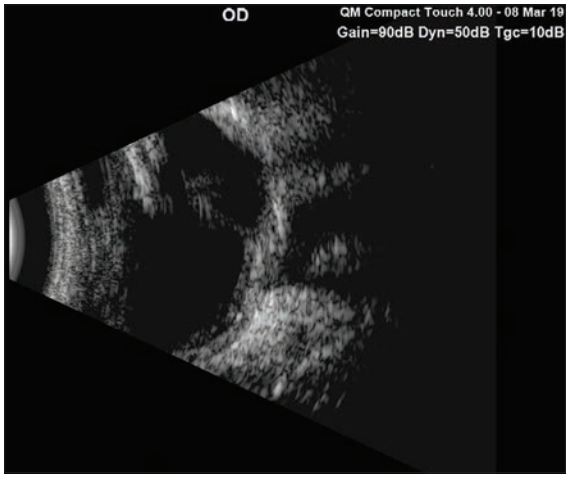


Figure 2: B scan ultrasonography showing nasal choroidal detachment and thickened choroid

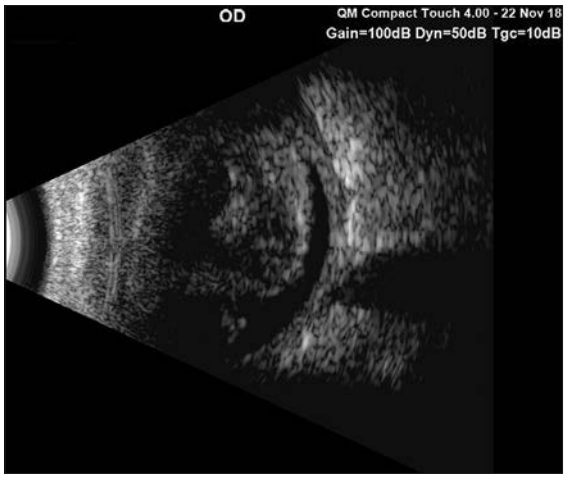


Figure 3: B scan ultrasonograph of right eye showing vitreous opacities and choroidal thickening

uveitis, a differential for EFE.[7] Oral steroids increased inflammation. As ophthalmologists, it is imperative that we investigate risk factors such as recent hospitalization or surgery. Patients, too, may not attach much significance to a recent hospitalization. The ophthalmic signs may be minimal and subtle at presentation.[8] Consequently, a high index of suspicion of fungal endophthalmitis is required in patients with predisposing factors where blood cultures are frequently negative.[4] The rate of misdiagnosis of EFE is as much as 50%.[7] It is, therefore, critical to improve awareness of this condition and to reduce the incidence of its misdiagnosis. Another challenge in treating EFE is the delay in presentation.

By using a PCR-based technique, we were able to rapidly diagnose EFE. PCR-based methods offer the possibility of establishing an etiologic diagnosis in less time than standard cultures[9] and because they can detect very low numbers of DNA copies, they have the potential to be extremely sensitive.[10] In addition, in intraocular infections, the relatively small volume of sample that can be obtained at any one time and the broad range of infectious pathogens make a PCR-based technique very useful.

CONCLUSION

The subacute nature of early infection in EFE makes early diagnosis challenging. It is, therefore, critical to improving awareness of this condition among ophthalmologists to reduce the incidence of its misdiagnosis. When patients with predisposing factors, hospitalized or ambulatory, present with uveitis, EFE should be considered as a probable differential, especially if the progression of signs and symptoms are seen despite treatment. A PCR based diagnosis of the vitreous specimen is extremely useful, as it can establish a rapid etiologic diagnosis, even in culture-negative patients. This technique could allow the institution of prompt appropriate therapy to improve patient's outcome.

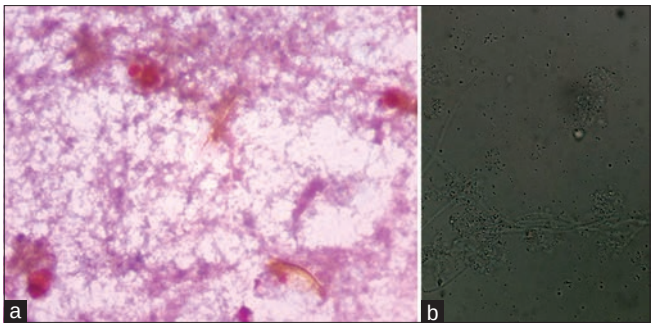


Figure 4: Cytology preparation from vitreous specimen demonstrating fungal hyphae in (a) gram staining and (b) KOH test

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.

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Conflicts of interest

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Case Report

Complete eyelid loss due to dog bite: A rare presentation

ABSTRACT

A 46-year-old male presented with a history of dog bite to the left eye. Examination revealed complete loss of the left upper eyelid with loss of the upper punctum and the surrounding tissue with extensive tissue damage. Anterior segment examination revealed an irregular epithelial defect, and the rest of the findings were unremarkable. After a thorough assessment and cleaning, anti-rabies immunoglobulin injection was given around the wound and anti-rabies vaccination schedule was started. Locally the eye was covered with plastic shield to prevent exposure after instillation of homatropine eye drop as a cycloplegic and chloramphenicol eye ointment as a broad-spectrum antibiotic. Systemically amoxicillin-clavulanic acid and metronidazole was started. Daily dressing was done for about a week. Once signs of healing were seen, the patient was posted for multi-step lid transplantation.

Keywords: Dog bite, eyelid loss, rare presentation

INTRODUCTION

Dog bites are not uncommon. However, most of these dog bites involve the upper and lower limbs. Dog bite to the head and face is more common in children. Ocular injuries due to dog bite are uncommon. Literature search did not reveal any case of dog bite causing complete upper lid loss and hence, we report this interesting case.

CASE REPORT

A 46-year-old-male presented to the emergency department with 2-h history of dog bite to the left eye as the patient was found over the floor under the influence of alcohol.

Examination revealed complete loss of the left upper eyelid starting from the medial canthus involving the upper lacrimal punctum up to the lateral canthus and superiorly involving the brow area [Figure 1)]. Anterior segment examination revealed central, corneal, 4 mm × 3 mm, irregular epithelial defect, and rest of the findings were unremarkable. Visual acuity in the left eye was 6/60 and in right eye was 6/6 by Snellen's chart.

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The wound was thoroughly washed with saline and irrigated with 5% betadine solution. Anti-rabies immunoglobulin 20 IU/kg was injected around the wound. Intramuscular anti-rabies vaccination schedule was initiated. Because the wound was secondary to dog bite with extensive tissue loss, the wound was unrepairable with simple suturing. The eye was covered with a plastic shield with homatropine eye drop and chloramphenicol ointment. Tetanus toxoid intramuscular injection was given. Systemic antibiotics such as amoxicillin-clavulanic acid and metronidazole were given. Daily dressing with 5% betadine was done BD, with frequent lubricant eye drop instillation. Slough noted on days 3 and 4

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Figure 1: Coloured photograph showing complete loss of upper eyelid with soft tissue loss



Figure 2: Coloured photograph showing lower lid rotational flap for upper lid transplantation

was debrided with the blunt end of a blade and thoroughly irrigated with 5% betadine. Once signs of healing were noted, the patient was posted for multi-step lid transplantation, which included lower lid rotational flap [Figure 2].

DISCUSSION

Ocular injuries secondary to dog bite are uncommon.[1,2] Injuries sustained in the area of ocular adnexa and lids due to blink reflex bear the brunt of dog bite injury.

Since ocular injuries secondary to dog bite are rare, they are more commonly seen in children than adults.[3]

Complete eyelid loss secondary to dog bite injury is extremely rare. Dog bite injury to the ocular area is considered Category 3 injury. Dog bite injuries are almost always contaminated by various microorganisms and cause high risk of local infection[1,4] as well as rabies. To prevent infection of the wound, it should be cleaned meticulously to remove any foreign body with copious saline and antiseptic solution such as 5% povidone iodine solution[1,5] (as it is safe for contact with ocular surfaces). Patients should be treated with systemic and local broad-spectrum antibiotics, anti-rabies vaccination, local anti-rabies immunoglobulin, and tetanus toxoid injection.

Function of the upper eyelid is blink reflex, which helps in spreading the tear film, prevents evaporation of tears, and protects the eye from dust/foreign body from entering.[1,6] When there is complete eye lid loss, all the above-mentioned functions are hampered, which can lead to exposure keratopathy, corneal ulceration, corneal melt, and dry eye disease.[7] Hence, early lid transplantation is important to avoid the above complications.[8] Complete upper eyelid loss carries high risk of complications and poor prognosis.[9]

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.

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Case Report

Pseudoxanthoma elasticum: Pathognomonic ocular and skin lesions with histopathological confirmation

ABSTRACT

A 34-year-old female presented to us with complaints of decreased vision in her left eye for 1 month. Best-corrected visual acuity was 20/20 in the right eye and 20/60 in the left eye. Anterior segment examination was normal in both the eyes. Fundus examination showed angioid streaks and comet tail lesions in both eyes. The left eye in addition showed a choroidal neovascular membrane (CNVM) at the macula. Systemic examination revealed skin lesions on the neck with a plucked chicken appearance and multiple papules. Biopsy from the lesions provided histopathological confirmation of pseudoxanthoma elasticum (PXE). CNVM in the left eye was treated successfully with a single dose of intravitreal bevacizumab injection with no further recurrence. No cardiovascular association was found in our case. This case report describes the pathognomonic fundus lesions seen in PXE. This case also emphasizes the need for thorough systemic evaluation, including biopsy from skin lesions for histopathological confirmation of the diagnosis in all cases with ocular features of PXE.

Keywords: Angioid streaks, choroidal neovascular membrane, comet tail lesions, pseudoxanthoma elasticum

INTRODUCTION

Pseudoxanthoma elasticum (PXE) is a rare inherited multisystem disorder characterized by progressive calcification of connective tissue rich in elastic fibers which result in characteristic changes in the skin, eyes, and the cardiovascular system. Cutaneous PXE was first described in 1896 by Darier, who coined the term "pseudoxanthoma elasticum."[1] Bruch"s membrane, the outer retinal layer also contains elastic fibers which undergo a loss in elasticity with subsequent calcification leading to cracks known as angioid streaks.[2] However, it is the comet tail lesions that are considered to be pathognomonic of PXE and may appear earlier than other changes of PXE such as angioid streaks and Peau d'orange. Hereby, we report a case with the pathognomonic comet tail lesions in the fundus, characteristic skin lesions, and histopathological confirmation of the diagnosis of PXE obtained from biopsy of the skin lesions.

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CASE REPORT

A 34-year-old female presented to us with complaints of defective vision in her left eye (LE) for 1 month. On examination, her best-corrected visual acuity (BCVA) was 20/20 in the right eye (RE) and 20/60 in the left eye. Anterior segment examination was within normal limits in both eyes. Fundus examination revealed brownish-gray irregular lines of varying width originating from the optic disc and radiating outward in both the eyes, suggestive of angioid streaks along with multiple, small chorioretinal atrophies in the mid-periphery as well as in the posterior pole with a halo

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of pigment hypertrophy around them and a tail of localized retinal pigment epithelium (RPE) atrophy pointing towards the posterior pole, suggestive of the characteristic comet tail lesions described for PXE [Figure 1]. The left eye in addition also had secondary choroidal neovascular membrane (CNVM) in the foveal region with associated intraretinal fluid. Spectral-domain-optical coherence tomography of the left eye confirmed the presence of CNVM [Figure 2]. Fundus fluorescein angiography in both the eyes revealed variable staining of the angioid streaks with the predominance of hyperfluorescence. The comet tail lesions were seen as hyperfluorescent spots, with their hyperfluorescent tails pointing toward the disc. The macula in the left eye demonstrated a well-demarcated area of lacy hyperfluorescence with blurring of the margins in the late phase, suggestive of classic CNVM. The patient was administered intravitreal bevacizumab (1.25 mg in 0.05 mL) in the left eye for CNVM with no further recurrence of CNVM. On systemic examination, the lateral aspect of her neck showed the presence of plucked chicken appearance, while the back of her neck showed the presence of multiple papules [Figure 3]. The patient had undergone skin biopsy in order to confirm the diagnosis of PXE. The H and E staining showed the presence of numerous distorted, fragmented, tortuous, and irregularly clumped elastin fibers in the mid-dermis with features of progressive dystrophic mineralization seen on Alizarin Red staining, suggestive of PXE [Figure 4]. Cardiovascular system evaluation in the patient was normal.

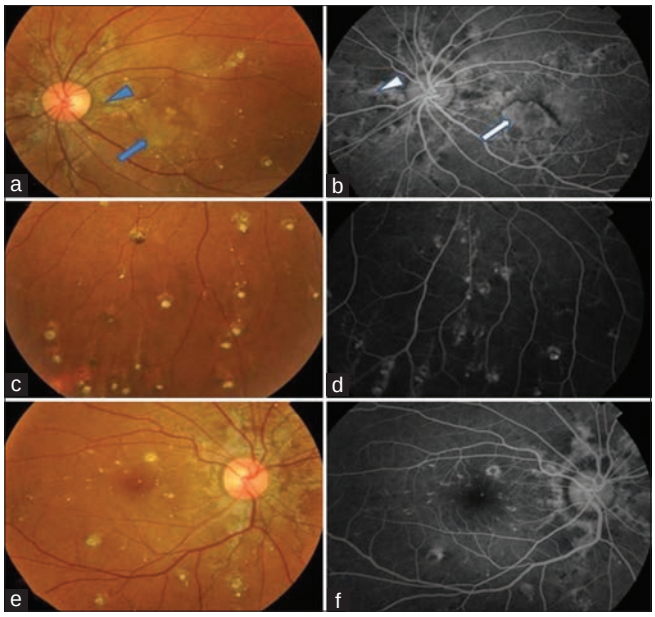


Figure 1: Fundus photograph (a) and fundus fluorescein angiogram (b) of the left eye showing angioid streaks (arrowhead) and choroidal neovascular membrane (arrow). Multiple comet tail lesions can be seen in the fundus photograph (c) and fundus fluorescein angiogram (d) of the retinal periphery. Fundus photograph (e) and fundus fluorescein angiogram (f) of the right eye showing angioid streaks and comet tail lesions

DISCUSSION

Skin is usually the first organ to be involved in PXE with the appearance of small (1–5 mm), yellowish ivory papules in large flexor surfaces – sides of the neck, axillae, groin, and back of the knee. Similar skin changes can also be seen in Paget's disease, beta-thalassemia, and long-standing focal cutaneous elastosis. A diagnosis of PXE can only be confirmed by a skin biopsy showing fragmented and clustered calcified elastic tissues in the middle and lower dermis, which was done in our case and revealed the same.[3-5] The ocular manifestations of the disease range from benign to vision-threatening complications. The first change usually appears in the form of pigment irregularities temporal to the fovea and is called Peau d'orange. It typically precedes angioid streaks by 1 to 8 years. Angioid streaks are breaks of the calcified and thickened Bruch's membrane. They are usually bilateral and surround the disc concentrically and radiate outward as brownish-gray irregular lines of varying width. Our case had the classic angioid streaks bilaterally. Secondary CNVM often develops in later stages of the disease due to fibrovascular ingrowth from the rim of angioid streaks.[6] Our case had CNVM in one eye and was treated successfully with one injection of intravitreal bevacizumab, and BCVA improved to 20/30 in the left eye with no further recurrence of CNVM till the last follow-up. CNVM due to angioid streaks usually shows favorable outcome with anti-VEGF injection, as seen in our case also.

Another more specific ocular finding in patients with PXE is the presence of comet lesions – small chorioretinal atrophies, usually occurring in the mid-periphery, with a localized atrophy of the RPE pointing towards the posterior pole from the lesion, just like a comet's tail. All these features

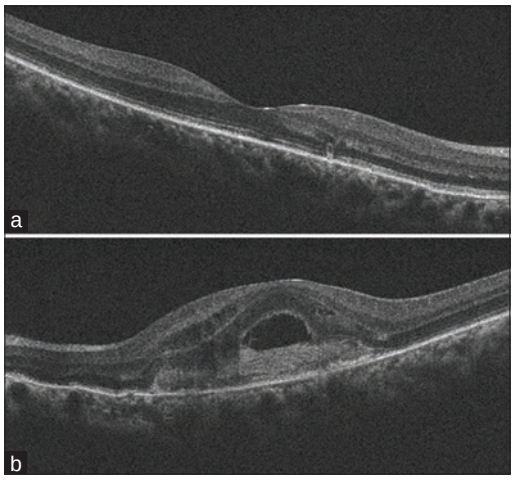


Figure 2: Spectral-domain-optical coherence tomography of the right eye (a) showing normal foveal contour and left eye (b) showing choroidal neovascular membrane with intraretinal fluid



Figure 3: Clinical photograph showing plucked chicken appearance on the lateral aspect of the neck (a) and the presence of multiple papules at the back of the neck (b) of the patient

were seen in our case. They have been suggested to be a pathognomonic clinical feature of PXE and can appear earlier than other changes of the pigment epithelium.[7] Other ocular associations for PXE include optic nerve head drusen and pattern dystrophy-like changes – none seen in our case.

As far as the systemic associations in PXE are concerned, the cardiovascular system is often affected – decreased peripheral pulse (25%), hypertension (22.5%), angina pectoris (19%), intermittent claudication (18%), and gastrointestinal hemorrhage (13%).[8] None of these were, however, present in our case.

PXE is, thus, an inherited multisystem disorder with important ocular and systemic associations. Although angioid streaks are a striking ocular feature of this disease, comet tail lesions are more pathognomonic of PXE, while skin biopsy is the only confirmatory test easily available. There is a need for thorough systemic evaluation including skin and cardiovascular systems, documentation and biopsy of any skin lesions present for histopathological confirmation of diagnosis in all cases with ocular features of PXE.[4,9,10] The clinical suspicion of PXE in our case is well supported by confirmatory skin lesion biopsy report, thereby ruling out any other mimicking clinical scenario. Although our patient did not have any cardiac problem at presentation, regular cardiovascular evaluation is advocated in all PXE patients to detect any abnormality at the earliest.

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.

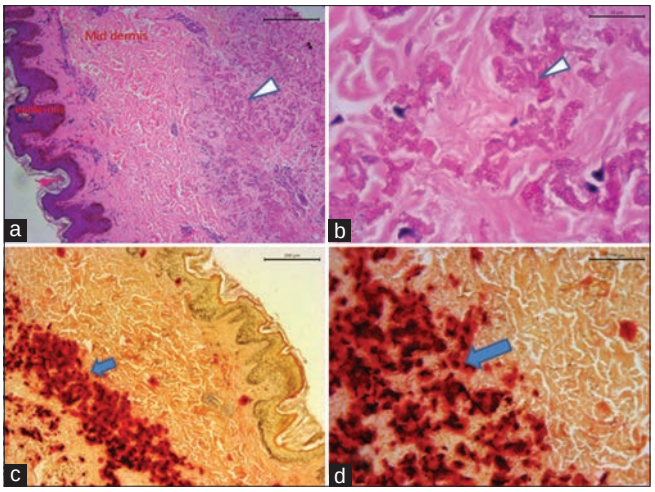


Figure 4: Histopathological features of pseudoxanthoma elasticum in cutaneous lesions: (a and b) fragmented elastic fibers (arrowhead) in the mid-dermis (H and E, ×10 and × 100), (c and d) fragmented elastic fibers with calcification and Alizarin red stain positive reactivity (×100 and × 200)

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Conflicts of interest

There are no conflicts of interest.

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Photo Essay

Fundus fluorescein angiography and optical coherence tomographic characteristics in acute multiple evanescent white dot syndrome

ABSTRACT

A 38-year-old female presented with a best-corrected visual acuity of 20/60 N18 and 20/20 N6. Fundus examination showed multiple yellow-white dots and spots at the posterior pole with disc edema and orange-yellow granularity at fovea. Fundus fluorescein angiography showed dots showing punctate hyperfluorescence and spots showing late staining and disc leakage. Optical coherence tomographic macula showed sub foveal hyperreflective elevated lesion on the retina pigment epithelium extending into the inner retina as far as the outer nuclear layer through disruption of inter digitation zone, ellipsoid zone (EZ), external limiting membrane and hyporeflectivity, and disruption of ELM and EZ corresponding to parafoveal lesions (predominantly spots).

Keywords: Fundus fluorescein angiography characteristics, multiple evanescent white dot syndrome, optical coherence tomographic characteristics

CASE REPORT

A 38-year-old female presented with best-corrected visual acuity of 20/60 N 18 and 20/20 N6 after a flu-like illness. She had photopsia, scotoma, and decreased vision in the right eye. Fundus photo and fundus photo montage showed multiple yellow-white dots nasal to macula and close to disc and spots at the posterior pole with disc edema and orange-yellow granularity at fovea [Figures 1 and 2]. Fundus fluorescein angiography (FFA) showed dots revealing punctate hyperfluorescence starting in the early choroidal phase in an incomplete wreath pattern and continuing in the arterial phase [Figure 3] and spots revealing hyperfluorescence of the margins in the early phase which stain in the late phase. Disc leakage was evident [Figure 4]. Optical coherence tomographic macula showed sub foveal hyper reflective material extending into the outer nuclear layer through disruption of external limiting membrane (ELM), ellipsoid zone (EZ), and inter digitation zone [Figure 5]. Parafoveal region showed disruption and mashed up ELM and EZ corresponding to the spots [Figure 6].

DISCUSSION

Unilateral presentation, female preponderance, flu-like illness and clinical findings at the level of retina pigment epithelium (RPE), not going beyond major vascular arcades in multiple evanescent white dot syndrome (MEWDS) are consistent with the lines of Jampol *et al*.[1] Gross *et al*. classified MEWDS into dots (approximately 100 μm) localized to deep retina and RPE and spots ($\geq$200 μm) localized to RPE and inner choroid. Dots show punctate hyperfluorescence in the

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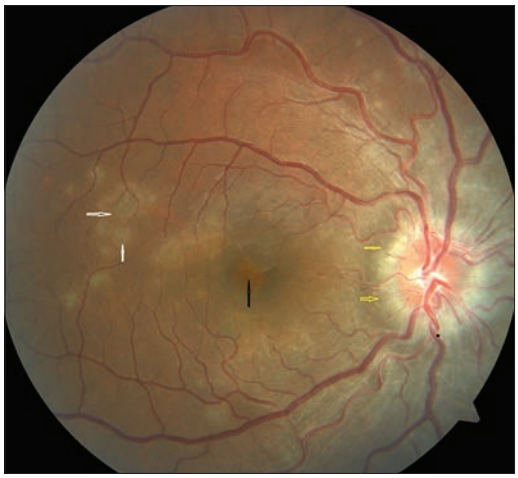


Figure 1: Fundus photo showing dots nasal to macula and close to optic disc (yellow arrow), spots in the para macular and posterior pole (white arrow) and orange-yellow granularity at the fovea (black arrow)

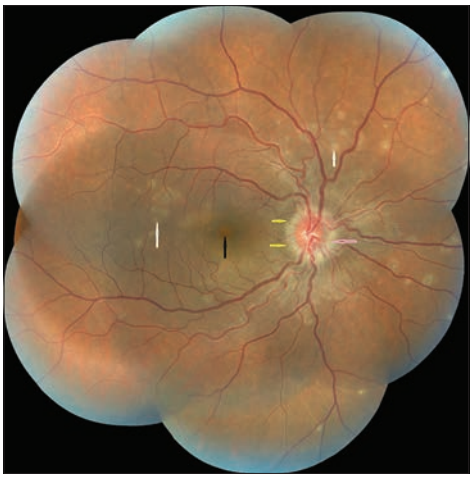


Figure 2: Fundus photo montage showing dots nasal to macula and close to optic disc (yellow arrow), spots in the para macular and posterior pole (white arrow), orange-yellow granularity at the fovea (black arrow) and optic disc edema (pink arrow)

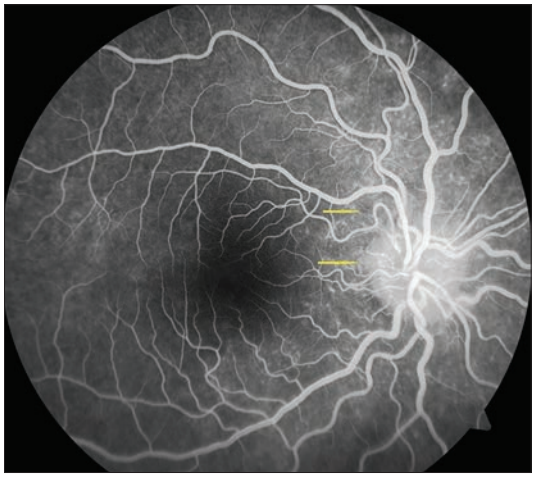


Figure 3: Dots showing punctate hyperfluorescence starting in the early phase and extending into the arterial phase nasal to macula and close to disc (yellow arrows)

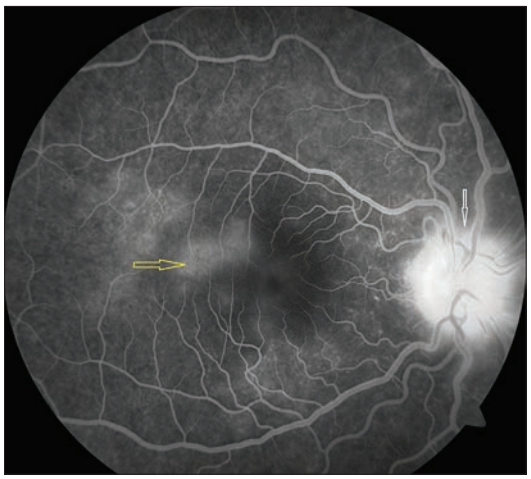


Figure 4: Late phase of fundus fluorescein angiography showing staining of spots temporal to macula (yellow arrow) and disc leakage (white arrow)

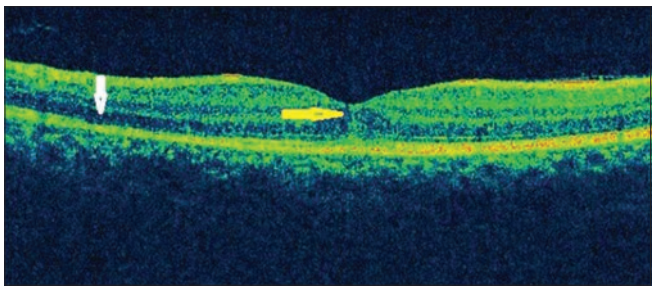


Figure 5: Optical coherence tomographic macula showing subfoveal hyperreflective lesion extending into the outer nuclear layer through disruption of ellipsoid zone, inter digitation zone and external limiting membrane (yellow arrow) and disruption of external limiting membrane and ellipsoid zone in the parafoveal region (white arrow)

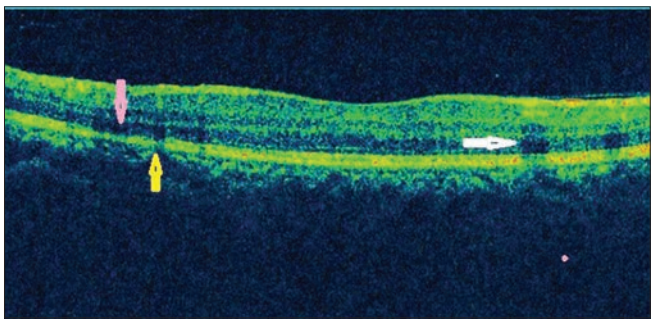


Figure 6: Optical coherence tomographic macula showing hyporeflective lesions corresponding to spots (yellow arrow), disruption of retina pigment epithelium (white arrow) and discontinuity of external limiting membrane, inter digitation zone, and ellipsoid zone (pink arrow)

choroidal as well as in the retinal artery perfusion phase. This is explained by the window defects generated by perfusion of choriocapillaris through the inflammatory lesions causing disruption of RPE and retinal capillary microangiopathy.[2] Spots are believed to be due to infiltration within RPE and inner choroid with inflammatory cells without significant ischemia.[2] The normal appearance of choriocapillaris points the possible injury at the level of outer retina and

photoreceptors. The inhomogeneity, attenuation of signal, and disruption of EZ may be due to inflammatory swelling of photoreceptors or RPE-photoreceptor complex and corresponded to spots resting on the RPE and dots if they extended into the inner retina and this could be correlated to FFA.[3-5]

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.

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Smartphone microscope in eye clinic to visualize fungus and Demodex

ABSTRACT

Purpose: Ophthalmologists often need to use a compound microscope to see slides of corneal scrapings, Demodex blepharitis, histopathology, or tear ferning test for diagnostic purposes. While such a microscope may be available in tertiary care centers, most eye clinics do not have it due to cost, space required, and infrequent use. These tests are often not done or delayed till a tertiary referral is possible. We demonstrate an alternative method using smartphone and an inexpensive attachment. **Materials and Methods:** Using the smartphone microscope attachment, the authors were able to capture excellent photographs and videos of corneal scrapings, histopathology, and Demodex. Photographs of the same slides were taken with a standard compound microscope as well. Trypan blue dye was used for staining the corneal scraping specimens to make the fungal hyphae in it clearly visible. **Results:** Photographs and videos captured by the smartphone microscope were compared with those from a compound microscope and found to be of adequate quality. They were determined to be good enough for diagnostic use. **Conclusions:** We determined that smartphone microscope attachment can be a useful adjunctive diagnostic tool for eye clinics corneal scrapings, histopathology, and Demodex, perhaps even for more applications.

Keywords: Corneal scraping, Demodex blepharitis, fungal hyphae, histopathology, smartphone microscopy

INTRODUCTION

Microscopes are very important and indispensable tools in ophthalmology.[1] Common uses include slit lamp biomicroscope in eye clinics, surgical microscope in operating rooms, and compound microscope for microbial/histopathological specimens.

With ubiquitous availability of smartphones, several innovations[2] have been described incorporating them for ophthalmic devices for slit lamp and fundus photography.[3,4] A smartphone is easy to handle, can be carried in a pocket or purse, and is a portable alternative to conventional expensive diagnostic devices. In ophthalmology, slit lamp adapters have even been three-dimensional printed[5,6] for smartphone slit lamp photography and fundus photography.[7] Magnifiers attached to smartphones have been described as a method to identify microorganisms.[8-10] It is reported that a smartphone with a simple attachment allows 1.5-µm resolution with satisfactory image quality.[11] Various magnifying attachments and miniature lenses[12] have been attached to cameras of smartphone without any alteration in hardware.[13] Medical Hackathons[14] have greatly helped in the development of

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low-cost innovations, and smartphones have greatly helped in affordable access to the technology needed.[15] Thus, smartphones help in biological imaging, other points of care diagnostics, monitoring, progression, and assessing treatment. Some of this diagnostic capability has been enhanced by artificial intelligence[16] to identify, for example, malarial parasite in blood smear.[17] Herein, we demonstrate utility of a commercially available smartphone microscope attachment Nurugo Micro (Nurugo, Seoul, South Korea) in various clinical situations in routine eye clinics. This device can be used to diagnose Demodex blepharitis, demonstrate the presence of hyphae in fungus keratitis, tear ferning test,[18] and for examination of histopathological slides of ocular specimens.

MATERIALS AND METHODS

Nurugo Micro (Nurugo, Seoul, South Korea) magnifying attachment is a small device (3.5 cm × 2.0 cm × 0.5 cm) which can be clipped onto the smartphone camera to act as a histopathology microscope. It utilizes smartphone flash for illumination which directs the light with a patent-pending light guide, and thus, it does not require a separate light or battery. It contains two polarizing filters, one in front of the flash and another placed in between the magnifying lens and camera lens. This arrangement of polarizing filters reduces glare from the visualized slide. The smartphone camera is used for capturing microscopic images with the help of an app, Nurugo Box, which has features for measurement as well.

We tested the device on various models of Android and iPhone smartphones (for example, Samsung Galaxy S8, S9, Note 9, iPhone 6, 7, SE, X, XS) which had single, dual, triple, and quadruple cameras and had no problems with illumination as the light guide works with the flash position up to 1.5 cm away from the camera. However, this would not work on smartphones which do not have a flash [Figure 1].

RESULTS

We evaluated the utility of this pocket microscope device as an adjunctive diagnostic tool in our eye clinic. We were able to establish its diagnostic value in three clinical situations which routinely otherwise need a histopathology compound microscope or laboratory services. We compared the same to pictures taken with a histopathology compound microscope [Figures 2-4].

Demodex blepharitis

It is an entity characterized by infestation of eyelashes by mites[19] of genus Demodex and is more commonly seen in patients with blepharitis.[20] The diagnosis is usually established by examination of epilated eyelashes under the microscope. Briefly, the eyelashes with scaly deposits at their bases, especially cylindrical dandruff, are epilated with forceps under the slit lamp magnification. The eyelashes are placed on a glass slide and covered with a coverslip. After initial examination, few drops of normal saline are added with a pipette or a small syringe to the margins of coverslip to loosen the debris. This helps in freeing of mites from the debris and hence better visualization. This procedure is routinely done by corneal surgeons to establish the diagnosis of this otherwise often undiagnosed entity. We found that this pocket microscope can be useful in visualizing these mites on the slides and capturing their images, although the contrast and other details were less clear as compared to the histopathology microscope.[21] [Figure 2].

Fungal hyphae

Identification of fungal hyphae in corneal scrapings by use of 10% (potassium hydroxide [KOH]) is a routine procedure in establishing the diagnosis of fungal keratitis which can play a critical role in guiding the treatment of these patients. Corneal scrapings are taken with a blade or needle from the base and margins of the ulcer and then placed on a glass slide. A 10% KOH solution is added to the material, and the specimen is examined after 5–10 min under the microscope. Although this is a routine procedure, it requires histopathology microscope and laboratory backup, which may not be always available, especially in peripheral or rural centers. We were initially unsuccessful in imaging the hyphae with this pocket microscope probably because of a lack of contrast between the hyphae and background illumination. It was likely because of the difference in illumination system between the histopathology microscope and smartphone



Figure 1: Smartphone and Microscope attachment. (a) Smartphone iPhone 7 and Nurugo microscope attachment. (b) Back view of attachment fixed on smartphone. (c) Side view of the attachment fixed on smartphone. (d) Demonstration of slide examination with Nurugo attachment

microscope. In the histopathology microscope, illumination is provided by the bulb at the base, and light passing through the slide is picked up by the examiner through the viewing lenses of the microscope. On the other hand, Nurugo device uses the smartphone light which is on the same side of viewing lens. Hence, the contrast here is insufficient to pick up hyaline fungal filaments on 10% KOH stain. However, we found that adding a drop of trypan blue dye, which is routinely used for capsular staining in cataract surgery, stains the walls of these filaments blue and allows easy visualization of the hyphae[22] [Figure 3 and Video 1].

Histopathology slides

Another useful feature of this device is its utility in examination and photography of the histopathology slides [Figure 4 and Video 2]. Quite often, ophthalmologists would like to see and review the slides of surgical specimens generated and sent to the pathology laboratory and it may not always be possible to visit pathology laboratory for review of these slides. We found that with this Nurugo device, it is quite possible to decipher the relevant details of various ocular pathology slides. Furthermore, the zoom function incorporated in the accompanying app allows examination and photography or videography of the specimen in different magnifications. The pictures and videos can be saved and shared easily for teaching, research, or teleconsultation purposes.

DISCUSSION

Nowadays, smartphones have become an indispensable part in the life of any medical professional including ophthalmologists. With the innovative use of various commercially available attachments, smartphone technology can offer cost-effective solutions or alternatives in different areas. The smartphone has become an indispensable tool for ophthalmologists and has been found to be a useful adjunct in various diagnostic procedures, tool for personal and patient education, and as a tool or various office-based calculations.[23,24] The device can be purchased online and costs around $40.[25] Hence, it offers a much cheaper alternative to histopathology microscope which would cost over $500. It is also very portable due to its very small size (3.5 cm × 2.0 cm × 0.5 cm) and can be carried in a small pocket along with the smartphone. It can also be set-up quickly and aligned due to the clip-on attachment.

The use of a smartphone with pocket magnifier has been previously reported by Agarwal *et al*. in this same journal to demonstrate stained fungal hyphae in scrapings of patients with fungal keratitis.[26] Although it was cheaper ($6 in 2015), the magnifier used in their study was a bigger battery-operated device with a light. It was 3.0 cm × 1.8 cm × 8.2 cm in size compared to 3.5 cm × 2.0 cm × 0.5 cm for the Nurugo device we used, making it 16 times bigger than our setup.

This is because the older device used much larger optics, lower dioptric power, and needed a battery and light, whereas the magnifier we used redirects camera flashlight to a diffuse glow with a patent-pending light guide and also uses high power aspheric optics. In addition, this device uses polarization filters to reduce glare and artifacts.

In their report, Agarwal *et al*. used lactophenol cotton blue (LPCB) and Gram staining to stain slides for fungal hyphae. LPCB and Gram stain are not easily available to an ophthalmologist whereas we can easily obtain trypan blue as leftover from cataract surgery. Therefore, in our study, we used trypan blue dye to stain the hyphae and capture it

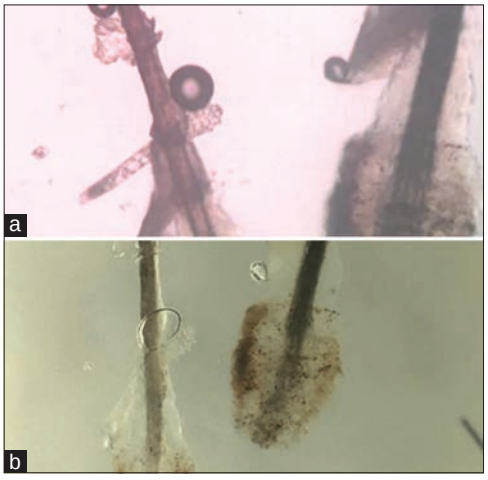


Figure 2: Demodex mites. (a) Seen through histopathology microscope. (b) Seen through Nurugo microscope attachment

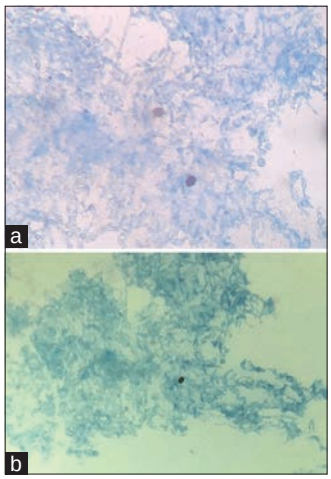


Figure 3: Fungal hyphae stained with trypan blue dye. (a) Seen through histopathology microscope. (b) Seen through Nurugo microscope attachment

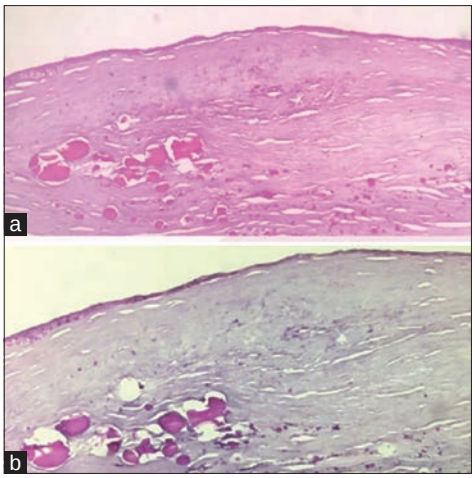


Figure 4: Histopathology view of spheroidal degeneration in a section of the cornea. (a) Seen through histopathology microscope. (b) Seen through Nurugo microscope attachment

with the Nurugo device making the whole process easier. With this stain, we were able to stain the hyphae and capture good-quality pictures of the stained hyphae [Figure 3]. We also noted a new publication by Dr. Prithvi Chandrakanth *et al*. in the Indian Journal of Ophthalmology, where they describe a homemade smartphone microscope attachment made out of four intraocular lenses and a flashlight.[27] The device they made was about the same size as the device we used, not including the flashlight, which makes their setup much bigger than ours. The novel, patent-pending light guide eliminates the need for a separate source of illumination in our case.

We also report the novel use of this pocket microscope to detect Demodex mites in epilated eyelashes [Figure 2]. This should be helpful in establishing the diagnosis of Demodex blepharitis in situations where histopathology microscope is not available.

CONCLUSIONS

In conclusion, we report the application of smartphone-based microscopic imaging in three key clinical entities which can be of great clinical significance in routine ophthalmic practice – Demodex blepharitis, fungal hyphae, and histopathology slides. Further studies may help in establishing the accuracy and cost-effectiveness of these innovative systems in these and other areas of ophthalmology.

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Conflicts of interest

There are no conflicts of interest.

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The Ophthalmologist who won the Nobel Prize and declined one too

Declining a Nobel Prize is not something that anybody would do in normal circumstances and is sure to cause controversy and consternation. However, nothing of that sort happened when it was quietly done for the first time by an ophthalmologist. In fact, it was considered a wise decision as he collected the same prize in another field which was closer to his heart.

The events that led to this interesting piece of history unfolded in 1911, when the Nobel Committee for Physics, decided to give the Physics Nobel to Allvar Gullstrand for his work in Geometrical Optics.[1] This was not surprising and considered overdue as Gullstrand was nominated for the same in the previous year also. At the same time, the Nobel Committee for Physiology or Medicine decided that they were going to award the Nobel Prize for Medicine to Gullstrand[1] for his works concerning the "Dioptrics of the Eye." The prospective awardee came to know of this and declined the Nobel in Physics so that he would get the other Nobel Prize. He himself was a member of the Physics Nobel Committee and so could do it discreetly. The Physics Committee then changed its report, this time including Gullstrand as one of the signatories suggesting Wilhelm Wien for the prize in Physics while the Nobel Prize in Medicine or Physiology went to Gullstrand.

Allvar Gullstrand MD (1862–1930) [Figure 1] thus became the only ophthalmologist, who got a Nobel Prize for work connected with ophthalmology and the only individual with a claim to what is described in the title of this article. (There are 2 other Nobel prize-winning ophthalmologists namely Fritz Pregl, MD of Austria in 1923 and Walter Hess, MD of Switzerland in 1949, but these were for nonophthalmology works by scientists who had given up ophthalmology and moved to other areas.)

The fact that Gullstrand was eligible for a Nobel prize in Physics, as well as Medicine at the same time speak volumes about the unparalleled and astounding scientific work of the great man.

MATHS TO MEDICINE

Many brilliant scientific and mathematical minds have found primary education very stifling and unstimulating as a result of which they have been labeled as poor and often impossible students. Those brilliant young minds naturally grew up hating their schools. Albert Einstein and Thomas Alva Edison are prime example to this. Allvar Gullstrand also belonged to that category. He was born on June 5, 1862, in Landskrona, a small town in Southern Sweden as the eldest son of a respected physician, Pehr Alfred Gullstrand. He obtained his primary education in Landskrona and found roaming in the streets as a prankster preferable to going to school. However, things changed when the family, probably disappointed with the school moved to Jönköping. A brilliant mathematics teacher in this town recognized Gullstrand's mathematical genius and managed to challenge the ever-demanding Allvar Gullstrand with university-level mathematics. Infinitesimal calculus and other advanced mathematical procedures followed soon,[2] and were eagerly lapped up by the hungry student.

It was only natural that Gullstrand wanted to study Engineering but then was persuaded by his father to take up medicine. He entered the faculty of medicine at the University of Uppsala in 1880. His interest in Physics and Mathematics probably channeled his interest toward ophthalmology with its optics, lenses, etc. Even before graduation, he went to Vienna to learn ophthalmoscopy, otoscopy, and laryngoscopy and spent 1 year there. He completed his graduation in 1888 and then to specialize in ophthalmology entered the ophthalmology clinic of the Seraphim Hospital in Stockholm as an assistant to Johan Widmark. He had entered the Medical school possessing a skill set seldom found in medical students-university level knowledge in advanced mathematics and a sound grasp of infinitesimal calculus. His analytical mind pondered over several scientific problems and questioned established theories. One of those areas was optics and refraction.

He found the Strums' conoid an oversimplification of things and therefore not correct in most of the eyes. As per Gullstrand, Strum had not included most of the higher-order aberrations which are there in most eyes and including those will have given different results. So when he was presented with an opportunity to do some research in the form of his thesis for his MD, he zeroed in on exactly

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this area. His calculations and experiments were based on advanced mathematical principles and calculus and naturally completed his thesis without anybody to guide him. Well nobody could have even if they tried. He proved his assumptions and demonstrated to the world, how the light ray bundles actually refracted in the complex reality of the eyes as opposed to infinitesimally thin theoretical lens systems. The Strum's conoid is useful in explaining what astigmatism is and it has therefore stood the test of time in basic medical teaching. However, Gullstrand's thesis showed that it is misleading and useless as a description of what a pencil of light is like when passing through the optics of an astigmatic eye.[2] The thesis received the highest grade and probably shaped Gullstrand's life from then on, as for the remainder of his active life he was eternally in love with optical problems and optical instruments. Honors and recognitions chased him constantly. In 1891 itself, immediately after his MD, he was appointed as Lecturer of ophthalmology at the Karolinska Institute in Stockholm. In 1894, the Uppsala University reached out to him and appointed him as their first chair and professor of ophthalmology, which was a great honor. He was just 32 years old at that time and got the position without having to apply for it.

His landmark work on astigmatism was only the beginning of his lifelong tryst with optics and physics. His next goal was to present a complete theory for the refraction of the eye. His first obstacle was that nobody precisely knew until then the exact shape of the cornea, the major refracting part of the eye. He designed a method for measuring this by photographing the corneal reflexes made by concentric rings or squares. The method was quite laborious and cumbersome but gave reasonably accurate results for Gullstrand. However, this formed the basis of corneal topography one century later when computerized processing of the images could be done. By 1900, Gullstrand presented his completed work on astigmatism, taking into account the higher-order aberrations also. The paper was very hard to read and comprehend and many of his mathematical derivations were not explained in detail, which led to some of his contemporaries remarking[2] that "Gullstrand is so shrewd that nobody can understand him."

GENTLEMAN

It was in 1901 that Gullstrand contacted the famous German Optical company Carl Zeiss in Jena for the feasibility of building a particular loupe for making precise measurements on photographs of the eye. To his pleasant surprise, M. Von Rohr at the company was able to build what Gullstrand wanted. Even though the "loupe" itself was very complex and expensive and hence did not sell, it turned his interest towards instrument design. Thus, began a lifelong successful collaboration between Gullstrand and the Carl Zeiss company. The Zeiss company made good microscopes useful for observing the surface of the eye, but not its interior. The inventive and intuitive mind of Gullstrand presented an idea to the Zeiss company–an idea which has ever since become the cornerstone of the modern ophthalmic examination: "illuminating the interior of the eye with a narrow bundle of converging light or a slit of light." The Carl Zeiss corneal microscope was fitted with Gullstrand's invention and the slit-lamp [Figure 2] was born. It was such a big contribution to ophthalmology and has been referred to as "the greatest gift to ophthalmology"[3] by many. Quite aptly in the 1922 American Society of Ophthalmology Congress, Washington, the president De Schweinitz, impressed with Gullstrand's demonstration of the device, remarked that from that time medicine had not only the Lady with the Lamp (Florence Nightingale), but also a male counterpart– the Gentleman with the Lamp (Allvar Gullstrand).[2]

The Gullstrand Carl Zeiss collaboration gave several other instruments to ophthalmology which had their place as



Figure 1: Allvar Gullstrand (source Wikipedia)



Figure 2: Gullstrand Slit lamp[2]

valuable diagnostic instruments in that time. Some of these were:

1. Gullstrand's grand stationary binocular reflexless ophthalmoscope in 1911

This then formed the basis of the similarly very successful Zeiss-Nordenson fundus camera (Nordenson 1925), the gold standard for several decades.

2. Gullstrand's Hand-Held ophthalmoscope
3. Gullstrand's Kartal Glasses, which were used for the aphakic eyes.

Gullstrand's contributions as a theoretical physicist and mathematician

Physics and Mathematics was Gullstrand's passion and this was what led him to optics and refraction and it is in this field that he made a lot of landmark contributions, some of which are as follows.[3]

Gullstrand's formula

The Gullstrand formula, (Dg e s = D_1 + D2–d/n × D_1 × D2) a well-known formula in optics, is still the gold standard when calculating the total refractive power of optical systems.

Gullstrand's schematic eye

Based on his very precise measurements of the human eye, Gullstrand gave the exact position of the cardinal planes of the optical system of the eye.[2] The information provided by the "Gullstrand eye" is still regarded as the gold standard today and can still be found in all training books for ophthalmology.[3]

Gullstrand's theory of physiological optics

It was Gullstrand's landmark work making use of complex mathematics that gave the world understanding about the refraction of light in the eye. He developed his theory of physiological optics based on his doctoral thesis on astigmatism and on Helmholtz's theories. It is for this contribution to the field of optics that he received the Nobel Prize.

HONORS IN GALORE

Unlike many inventors and scientists who were never properly honored during their primes, Gullstrand was fortunate to have received heaps of them and deservedly so from quite early in his career. The Nobel Prize for Medicine in 1911 was of course the most precious jewel in his crown, but even before that, he had received awards from the Swedish Royal Academy of Sciences, Centenary Gold Medal of the Swedish Medical Association, Bjorken Prize of the Uppsala Faculty of Medicine, etc. In 1914, the Swedish parliament, as requested by the Academic Senate of the Uppsala University created a personal chair in physical and physiological optics to relieve Gullstrand from routine hospital work and clinical teaching and allow him to devote his time entirely to research. The Graefe Medal of the Deutsche Ophthalmologische Gesellschaft which is only awarded every 10 years was given to him in 1927. For his sixtieth birthday, the Swedish Medical Society coined a Gullstrand medal in his honor and created a Gullstrand fund to promote ophthalmic research.

Several administrative, academic and honorary positions chased him most of which he refused because of his engagement in science. In 1905, Gullstrand was elected member of the Royal Swedish Academy of Sciences, the body that awards the Nobel Prizes in chemistry and physics (as well as economics since 1969). He first entered its medical section, but later moved to its physics section in 1911, continued as a member till 1929, and served as its chairman from 1923 to 1929. During the academic year 1925–1926, he was president of the Royal Swedish Academy of Sciences. The Swedish Medical association also gave him honorary membership.

GULLSTRAND AND ALBERT EINSTEIN

When Gullstrand received his first nomination for the Physics Nobel prize in 1910, there was another brilliant young scientist whose name also appeared along with. It was none other than the great Albert Einstein. However, if Einstein had to wait for 12 more years to get the Nobel despite being nominated 11 times during this period, it was mostly due to Gullstrand's opposition to the theory of relativity and finally, the award had to be given for his work on "Photoelectric Effect" and not for the theory of relativity.

Gullstrand took his vocation quite seriously and worked hard. He was an academician, a scientist, and a clinician all rolled into one. He sacrificed himself completely to research. How he managed his time surprised many and is answered by his own remark that "an academic teacher and scientist who is not trembling from exhaustion at the end of a semester has not done his duty."[2] He never slowed down and continued in this fashion until his death from a cerebral hemorrhage on July 28, 1930. The inscription on the coveted Gullstrand Medal, coined in his honor provides an appropriate epitaph for the man who illuminated the ocular chambers with the now indispensable slit-lamp-"Obscura Oculi Illustravit" which translates as "enlightening the darkness of the eye."[4]

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There are no conflicts of interest.

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FIVE-YEAR FOLLOW-UP OF FIRST ELEVEN PATIENTS UNDERGOING INJECTION OF CULTURED CORNEAL ENDOTHELIAL CELLS FOR CORNEAL ENDOTHELIAL FAILURE

Numa K, Imai K, Ueno M, Kitazawa K, Tanaka H, Bush JD, *et al*. Five-year follow-up of first 11 patients undergoing injection of cultured corneal endothelial cells for corneal endothelial failure. Ophthalmology 2021;128:504-14.

Penetrating keratoplasty, descemet stripping automated endothelial keratoplasty (DSAEK) and descemet membrane endothelial keratoplasty (DMEK) are the current surgical treatments for corneal endothelial failure. They require donor cornea, are invasive, and can result in early surge of endothelial cell loss, graft detachment, or dislocation. The corneal shape may not be well restored. Ideal is a surgical procedure that reproduces normal shape with high corneal endothelial cell density (ECD) with no structural irregularity with good postoperative visual acuity and proper corneal function for all types of corneal endothelial failure.

A novel surgical procedure of injection of cultured human corneal endothelial cells (hCECs) with Rho-associated protein kinase inhibitor to promote corneal endothelial cell (CEC) engraftment for the treatment of endothelial failure conditions was published earlier. The objective of the present study is to report the safety and efficacy of this novel cell injection therapy, a 5-year postoperative clinical data from a first-in-humans clinical trial group.

This was a prospective observational study involving 11 eyes of 11 patients with pseudophakic endothelial failure conditions with total corneal edema who underwent hCEC injection therapy between December 2013 and December 2014. That is, fuchs endothelial corneal dystrophy (FECD) (7 eyes), argon laser iridotomy induced (2 eyes), pseudoexfoliation syndrome keratopathy (1 eye), and intraocular surgery-related corneal edema with intraocular lens suturing (1 eye), and all with posterior chamber intraocular lens.

Three hundred milliliter of unique fluid-based cell suspension in modified Opti- MEM I Reduced-Serum Medium supplemented with Rho-associated protein kinase inhibitor was aspirated into a dead space-free syringe and then injected into the anterior chamber, with patients placed in a face-down position for 3 h to enhance the adhesion and engraftment of the injected cells. Systemic and topical steroids were given after the procedure.

All patients were examined at 1, 4, 12, 24 weeks and 1, 2, 3, 4, 5 years after hCEC therapy. Results showed ECD more than 500 cells/mm^2 in 10 of 11 eyes. Eight eyes had ECD more than 1000 cells/mm^2 and 2 had ECD more than 2000 cells/mm^2. The mean standard deviation of ECD at 3, 4, and 5 years was 1384 ± 451, 1268 ± 472, and 1257 ± 467 cells/mm^2, respectively. Coefficient of variation improved from 0.46 ± 0.076 to 0.37 ± 0.088 and percentage of hexagonality improved from 47 ± 8.7% to 54 ± 6.2% indicating that CECs stabilized over 5-year postoperative period. Guttae in FECD eyes had not changed or decreased in size and area as compared to at 6 months and 2 years. Corneal thickness at center was within the normal range (<630 μm) with a rapid decrease within 4 weeks, followed by a gradual decrease that was maintained up to 5 years and corneal epithelial and stromal edema completely disappeared in 10 eyes. Best-corrected visual acuity (BCVA) improved in 10 eyes (91%) and mean BCVA improved to 0.046 from 0.876 logarithm of the minimum angle of resolution before surgery. Surgery done for 1 eye with raised intraocular pressure (IOP) due to steroid-induced glaucoma at 8 months, followed by normal IOP in all eyes up to 5 years. There is no anterior uveitis or allogeneic immune reaction.

At 5 years, this novel therapy is thus equivalent in clinical outcomes to DSAEK and DMEK. Corneal transplantation requires one donor cornea to treat one diseased eye, while this allows for enough hCECs to treat at least 300 diseased eyes to be cultured from just 1 donor cornea. Limitations of the study are small number of eyes enrolled.

CONSENSUS NOMENCLATURE FOR REPORTING NEOVASCULAR AGE-RELATED MACULAR DEGENERATION DATA CONSENSUS ON NEOVASCULAR AGE-RELATED MACULAR DEGENERATION NOMENCLATURE STUDY GROUP

Spaide RF, Jaffe GJ, Sarraf D, Freund KB, Sadda SR, Staurenghi G, *et al*. Consensus nomenclature for reporting neovascular age-related macular degeneration data consensus on neovascular age-related macular degeneration nomenclature study group. Ophthalmology 2020;127:616-36.

Age-related macular degeneration (AMD) is a disease complex beyond 50 years of age, in which the structure and function of the macula deteriorates. A salient characteristic is the accumulation of extracellular deposits including subretinal drusenoid deposits, basal linear, and basal laminar deposits. In the early phases of AMD, only minimal visual changes. With time, vitelliform deposit accumulate,

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pigments migrate into retina, drusen size increase, and hypopigmentation and hyperpigmentation of the retinal pigment epithelial (RPE) develop. Late phases show atrophy of the outer retina, thinning and loss of the RPE, and macular neovascularization (MNV). MNV can lead to leakage, bleeding, and scarring as well as severe vision loss. The terminology used in most of the literature is based on fluorescein angiography (FFA). With better AMD knowledge by recent advances in imaging technology such as optical coherence tomography (OCT) and OCT angiography (OCTA), nomenclature system needs revision. To evaluate and standardize nomenclature for reporting AMD data, a consensus meeting of an international panel of retina specialists, imaging and image reading center experts, and ocular pathologists was organized under the auspices of the Macula Society, an international study group referred to as the Consensus on Neovascular AMD Nomenclature group. They discussed and codified a set nomenclature framework for classifying the subtypes of neovascular AMD and associated lesion components.

Type 1 MNV represents areas of neovascular complexes arising from the choriocapillaris into the sub-RPE space. OCT shows as an elevation of the RPE by material with heterogeneous reflectivity; vascular elements may be seen. OCTA shows vessels below the level of the RPE. Occult choroidal neovascularization (CNV) old term shows stippled hyperfluorescence over an area of elevated RPE, which expands to coalesce in the later phases of FFA. Indocyanine green angiography (ICGA) shows just late staining of the lesion, referred to as plaque. Polypoidal choroidal vasculopathy is defined by a branching vascular network and nodular vascular agglomerations. OCT findings similar to Type 1 MNV. Dilated vascular elements at the outer border of the lesion are apparent in OCT. Because of the slow perfusion dynamics, polyps remain undetected by OCTA. The pattern of the RPE elevation may suggest nodules in FFA. ICGA shows a branching vascular network with aneurysmal dilations. Late staining of tissue around the dilatations occurs. In Asian persons, the typical presentation comprises isolated macular involvement, unilateral, and male preponderance.

In Type 2 MNV, proliferation of new vessels arises from the choroid into the subretinal space above the level of RPE. Although these vessels traverse the sub-RPE space, the disease process is dominated by the subretinal portion. It is associated with exudation directly into the sub retinal space. OCTA demonstrates vascular elements above the level of RPE. FFA shows early, typically well-defined hyperfluorescence with late leakage. Type 2 MNV also seen in angioid streaks, lacquer cracks, and chorioretinitis.

Type 3 MNV refers to a downgrowth of vessels from the retinal circulation toward the outer retina. Thus, the term CNV is not accurate for Type 3 and shows extension of hyperreflectivity from the middle retina toward to level of the RPE associated with intraretinal edema, hemorrhage, and telangiectasis. ICGA shows a small hyperfluorescent lesion and represents descending vessels viewed axially. OCT shows varying amounts of intraretinal edema, subretinal fluid (SRF) and exudation, pigment epithelial detachment (PED). OCTA shows the downgrowth of new vessels toward or even penetrating the level of the RPE and also known as retinal angiomatous proliferation and shows focal hyperfluorescence associated with intraretinal staining.

Retinal-choroidal anastomosis is an aberrant connection between the retinal and the choroidal circulation. Course of vessel can be seen with OCT or OCTA. Although visible on FFA, ICGA is better. If prominent neovascularization is present in subretinal and sub-RPE compartments, the term mixed Type 1 and Type 2 neovascularization used. An eye with Type 3 disease that has penetrated the RPE monolayer without making an anastomosis with the choroidal circulation is said to have extension of Type 3 disease into the sub-RPE space. Some eyes show Type 3 neovascularization and a separate unconnected region of Type 1 neovascularization. This situation may be summarized as Type 3/1 neovascularization, in which the "/" is interpreted as meaning "and" in an independent sense.

Exudation is a common feature of MNV and can manifest in 4 basic forms: Leakage, SRF, lipid, and subretinal hyperreflective exudative material (SHRM). Leakage is the release of excess fluid and serum components as the result of the breakdown of the blood-retinal barrier.Detected with FFA, in which hyperfluorescence outside of vascular confines is seen to expand in area over the course of the angiographic sequence. The dye may accumulate in tissue, a process called staining, or into fluid-filled spaces, termed pooling. Intraretinal fluid may accumulate from retinal vasculature leakage or intraretinal neovascularization or diffusion of fluid through the outer retina related to abnormalities of the external limiting membrane (ELM) and associated structures. SRF is separation of the neurosensory retina from the RPE by fluid. Readily detected using OCT.

Lipid (or hard exudates) is lipoprotein precipitates related to chronic vascular leakage. Concentration of lipoprotein molecules may exceed their solubility, resulting in tissue deposition. SRHM is the exudation into or under the retina of material (include an admixture of serum, fibrin, and inflammatory cells) excluding red blood cells, detected

by color fundus photography. OCT appears as regions of featureless accumulations of relatively uniform increased reflectivity. SHRM is not hyperautofluorescent, as opposed to vitelliform material which is hyperautofluorescent. SHRM can resolve but fibrosis can occur in its wake. Presence of SHRM is associated with poorer visual outcomes. Clues to Type 2 MNV with SHRM include a classic pattern on FFA, disruption of the ELM, and intraretinal fluid. Reappearance of SHRM is a sign of recurrent exudative activity resulting from neovascularization.

Retinal PED is a clinically evident separation of the RPE monolayer from the underlying Bruch's membrane. This can occur from drusenoid material, serous fluid, neovascular infiltration, or blood. Collections of drusen material of more than 350 mm in diameter are called drusenoid PEDs. Serous PEDs are collections of fluid, but in AMD, serous PEDs typically are associated with neighboring MNV. Neovascular infiltration usually is associated with some element of fibrotic tissue and is called fibrovascular PEDs. Elevations with blood are called hemorrhagic PEDs. The RPE may be elevated by fluid released from the neovascularization, and this may occur eccentric to the neovascular tissue, producing a notched PED where the neovascularization is in the notch. OCT and OCTA can detect the internal anatomic structure of the PED, and OCTA particularly effective if the PED is shallow. PEDs can occur in the context of Type 1 or Type 3 MNV but not Type 2. The association with Type 1 may be related to the sub-RPE location of the vessels and potential exudation. Types 2 and 3 cause unknown.

Hemorrhage is an extravasation of blood from the neovascular complex and can be located in the sub-RPE, subretinal, intraretinal, and occasionally preretinal compartments. Fresh blood is red and hypoautofluorescent. As blood ages, it becomes yellow, does not stain during FFA and is hyperautofluorescent. Fibrosis refers to the apparent build-up of tissue (collagen) in any layers of the retina, including the subretinal space, RPE monolayer, or sub-RPE space. The fibrotic region typically stains on FFA and is not hyperautofluorescent. Rip (or tear) of the RPE is caused by a tractional dehiscence of the RPE monolayer following contracture of the sub-RPE fibrovascular tissue. It retracts producing a heaped-up region adjacent to a zone of absent RPE tissue. The retracted RPE monolayer causes decreased transmission to the deeper layer causing decreased fluorescence during FFA and choroidal hypotransmission with OCT. It is hyperautofluorescent because of the increased light path through fluorophores. Area of denuded RPE shows hyperfluorescence in FFA and ICGA and hypertransmission to the choroid on OCT. With the absence of the RPE, and likely atrophy of the choriocapillaris, flow signal can be obtained from deeper choroidal vessels in OCTA.

Outer retinal atrophy (ORA) is loss of the ellipsoid zone (EZ) and interdigitation zone (IZ) usually with corresponding loss of thickness of the outer nuclear layer (ONL) and occurs after prolonged SRF accumulation, regression of subretinal drusenoid deposit, or over large collections of drusen material. In complete ORA, the EZ and the IZ are not visible, the ELM may not be discernible, and ONL becomes thinner. In incomplete ORA, a discontinuous loss of the EZ has occurred, and the IZ is not visible. RPE and ORA refer to the absence of a clinically normal RPE monolayer, usually by cell death. In OCT imaging, RPE atrophy is characterized by a loss of the RPE band with associated choroidal hypertransmission. The loss of RPE cells usually is accompanied by concomitant loss of the outer retina. If the zone of abnormalities is more than 250 mm in diameter, it is termed complete RPE and ORA (cRPE and ORA). If the zone of abnormalities is <250 mm, or if the hypertransmission is fragmentary, it is termed incomplete RPE and ORA.

On substituting modern terms, late AMD would be cRPE and ORA that correspond roughly to geographic atrophy or MNV. Criticisms of this approach are that cRPE and ORA and MNV are different conditions with dissimilar pathophysiology, and therefore, they should not be lumped together. In conclusion, establishing a uniform set of definitions will facilitate comparison of diverse patient groups and different studies. The study group suggests that the consensus standards outlined in this article should be used in future reported studies of neovascular AMD and clinical practice.

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There are no conflicts of interest.

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Post trabeculectomy situations: Hypotony

ABSTRACT

Hypotony, characterized by a low intraocular pressure <6.5 mm Hg or <5 mm Hg with possible clinical complications, can lead to dreaded complications, posttrabeculectomy. It leads to a breakdown of blood-aqueous barrier, leading to an inflammatory cascade, scarring, and bleb failure, in the long term. It also predisposes to blebitis and other hypotony-related complications. Identifying the cause of hypotony, such as bleb leak or overfiltration, is vital to addressing the underlying cause. It can be managed conservatively with pressure patching, and medically with steroids or cycloplegics, or would require surgical bleb revision, depending on the cause and extend of underlying damage. In this article, we review the definition, pathophysiology, risk factors for hypotony, and posttrabeculectomy and identify the various possibilities, and their respective management strategies.

Keywords: Bleb leak, blebitis, hypotony, hypotony maculopathy, overfiltration

INTRODUCTION

Although low intraocular pressure (IOP) is a desirable outcome, the ocular effects of an IOP that is "too low" pose an even greater risk structurally and functionally. "Statistical" hypotony is defined as IOP >3 standard deviation (SD) below the mean (<6.5 mm Hg).[1] According to the Guidelines on Design and Reporting of Glaucoma Surgical Trials by the World Glaucoma Association, the accepted norm is a numerical cut-off of 5 mm Hg for non-physiological IOP, along with possible clinical complications that could compromise vision.[2] "Clinically significant" hypotony, on the other hand, is when a patient's IOP is so low that there is resultant visual loss. The reported incidence ranges from 1.6% to 12.4% in clinical trials and 7.2% to 42.2% in observational studies.[3]

Formation of a healthy, well-functioning bleb is essential for a successful outcome following trabeculectomy. The significance of this is demonstrated in an article by Benson *et al*.[4] where a 5-year survival showed evidence of a statistically significant difference ($P = 0.0492$) with patients in the hypotony group failing more rapidly than the control group. In addition, the number of trabeculectomies that failed in each study year, (most of which failed within the 1st year), were more in the hypotonous group.

The pathophysiology of failure is illustrated in Figure 1.

Hypotony has been postulated to an increased breakdown of the blood-aqueous barrier as compared to nonhypotonous posttrabeculectomy eyes, thus causing a release of inflammatory mediators into the aqueous and through the filtering bleb into the surrounding tissues.[4] These mediators are responsible for scarring of the underlying tissues, thereby resulting in failure of trabeculectomy.

Hypotony maculopathy is a sight-threatening complication characterized by chorioretinal folds, increased vascular tortuosity, and disc edema. Statistically, it implies that the IOP is 3 SD below the mean or IOP is <6 mm Hg.[5] It has a reported incidence of <1% to up to 30%. A lower

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incidence of 1.3% has been documented posttrabeculectomy with mitomycin C (MMC) 0.5 mg/ml for 5 min.[6] Causes of vision loss in hypotony maculopathy include (a) mechanical distortion of photoreceptors, (b) permanent changes in retinal pigment epithelium and neurosensory retina, and (c) hypotony-induced astigmatism. The identified risk factors include:[6-8]

- Young myopic males
- Use of antimetabolites (MMC >5FU)
- Primary trabeculectomy
- Higher preoperative IOP
- Preoperative use of oral CAI
- Caucasians >African-Americans.

Hypotony maculopathy is diagnosed clinically and with the aid of fundus fluorescein angiography where it is seen as alternating bands of hyper- and hypofluorescence due to the choroidal folding, and leakage from the optic nerve but not from retinal capillaries.[5] Optical coherence tomography could show retinal macular thickening with or without intraretinal cyst and serous.

The possible causes of low IOP posttrabeculectomy can be categorized based on anterior chamber (AC) depth and bleb height, as shown in Table 1.

BLEB LEAK

Reported incidence of an early bleb leak is 0 to 30%,[9] while that of a late bleb leak in thin cystic and avascular blebs is 5.2% to 6%, as compared to thick walled blebs where it is reported to be 1.1% to 1.3%.[10-14] The notable risk factors include (a) use of antimetabolites and (b) fornix-based incisions.[15] The characteristic features which are suggestive of bleb leak include:

1. Flat bleb
2. Shallow/well-formed AC
3. Seidel's positive

The usual cause for conjunctival buttonholes is the penetration of the tissue by the tip of a sharp instrument, which, in turn, usually occurs in cases with extensive conjunctival scarring such as chronic inflammatory conditions, prior external ocular surgeries. To diagnose a buttonhole intraoperatively, the conjunctiva should be carefully examined at the end of the procedure either by filling the AC and raising the filtering bleb and looking for an escape of multiple small air bubbles from the site of the defect, or with the use of a dye. The importance of identifying bleb leaks and treating them is due to its predisposition to (a) hypotony and related complications, (b) blebitis and endophthalmitis, and (c) bleb failure.[14]

Hypotony without a visible bleb should raise a suspicion of a possible leak, which can be confirmed by performing the Seidel's test, which helps in localizing the site of the leak. In this procedure, a fluorescein strip is used to paint the bleb, and the bleb is then visualized under high magnification on the slit-lamp biomicroscope to look for a stream of aqueous from the bleb surface. The outcome of this test can be categorized as follows, based on the amount of aqueous flow:

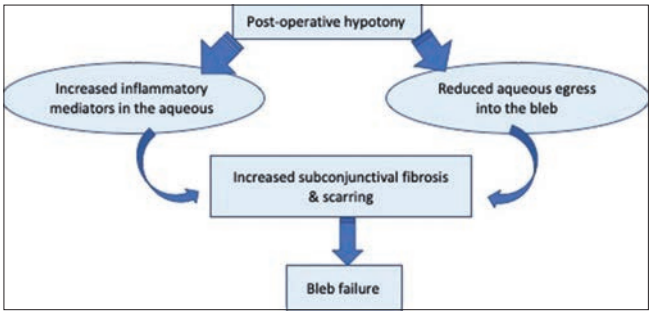


Figure 1: Pathophysiology of bleb failure due to hypotony



Figure 2: Ask the patient to look down and then apply the rolled torpedo bandage over the upper lid



Figure 3: Then patch the eye

Table 1: Causes of low intraocular pressure posttrabeculectomy

Well-formed AC		Shallow AC	
Flat bleb	**Well-formed bleb**	**Flat bleb**	**Elevated bleb**
Conjunctival wound leak	Expected outcome	Bleb leak	Overfiltration
Aqueous shutdown	Large diffuse bleb	Aqueous shutdown	
	Overfiltration	Serous choroidal detachment	
		Cyclodialysis cleft	
		Miscellaneous	
		Large scleral fistula	
		Retinal detachment	
		Extensive cyclodestruction	
		Inadvertent use of aqueous suppressants	

AC – Anterior chamber

Table 2: Classification of bleb leak based on onset

Early onset (within 2 months)	Late onset (beyond 2-3 months)
Usually heal spontaneously	Spontaneous late leaks more common in avascular thin blebs
Probable causes	Increased chances of (BRI) with these types of blebs
Surgical trauma	
Loose sutures	
Management	Possible risk factors
Prophylactic wide spectrum antibiotics	MMC (3.3%-10%)
BCL	Full-thickness procedures (3.3%)
Fibrin tissue glue	Indications for immediate surgical repair
Surgical revision	Severe hypotony
	Flat AC
	Vision loss
	Previous episodes of BRIs
	Management
	Surgical revision is preferred option

BCL – Bandage contact lens, BRI – Bleb-related infections, MMC – Mitomycin C, AC – Anterior chamber

Table 3: Classification of bleb leak based on features

First (uncomplicated) leaks	Second (complicated) leaks	Third (persistent) leaks
No other clinical features	Failed conservative measures	Recurrent blebitis/ endophthalmitis
	Visual loss	Recurrent bleb leaks with symptoms
	Hypotony	
	Loss of bleb height	
	Flattening of AC	
	Progressive thinning of bleb	
	Exuberant symptomatic bleb	

AC – Anterior chamber

a. Point leak (pinpoint staining of the conjunctiva)
b. Bleb sweating (transconjunctival ooze as pearls: also called physiological Seidel/pseudo-Seidel)
c. Frank bleb leak (stream of aqueous).

In a study by Gollakota *et al*.,[16] the importance of recognizing these patterns has been highlighted, as the sweating blebs are cystic, elevated, and still functional. At the same time, they carry a higher risk of complications prior to bleb repair (such as blebitis, hypotony, maculopathy), but a better bleb survival, post bleb repair, and thus benefit from an early intervention.

The site of leak marks the thinnest and most avascular area of the bleb. Histopathological examination in studies has suggested a breakdown of conjunctival epithelium with thinning and stromal necrosis in the concerned area.[17]

Bleb leaks can be classified based on (a) onset or (b) associated clinical features [Tables 2 and 3].

Conservative management

Initial treatment involves the use of pressure patch, in a method known as torpedo bandage, as illustrated in the pictures below.[1] The idea is to apply pressure over the bleb and not the eye [Figures 2 and 3].

The use of aqueous suppressants is debatable. The principle behind it is that it reduces the amount of aqueous that can flow through the leak, thus continuously disrupting epithelial healing.

Contact lenses

Soft contact lenses (CLs) have a visual and cosmetic advantage overpressure patching for these patients. The principles behind its use include: (a) It tamponades the area of aqueous leak, thus slowing or stopping aqueous flow and reduces mechanical aggregation from the lid, thus promoting epithelial restoration (b) It helps maintain good bleb morphology and function. These lenses can be left *in situ* for as long as 3 weeks. There are three properties which are important before dispensing contact lenses for the same:

i. Diameter:
- For defects close to or <2 mm from the limbus: 14 or 15.5 mm CL (12)
- For defects 2-4 mm away from the limbus: 17 or 20 mm CL (12).

ii. Modulus: Low
iii. Dk value: High.

Fibrin tissue adhesive

Specifically, in glaucoma literature, Asrani and Wilensky have been credited with describing the use of autologous fibrin tissue glue to treat bleb leaks.[18] Fibrin glue is a two-part admixture containing a protein base and thrombin–calcium chloride activating solution, containing fibrinogen, plasminogen, fibronectin, and factor XIII in bovine aprotinin solution. It has been postulated to create collagen crosslinking lending strength to tissue adherence through fibrin–fibronectin bonds, and thus help sealing leaking wounds. Its rapid activation time of 20–30 s makes it appealing for intraoperative use. It can be used either as a sequential method or simultaneously using Duploject. However, since fibrin glue requires a dry surface to be effective, its application over a continuously leaking bleb as was originally suggested was thought to prevent a stable fibrin clot formation. Thus, certain modifications have been suggested to avert the situation, by filling the chamber and bleb with air, thus increasing the surface tension of the air–aqueous interface as well as keeping the surface dry.[25] Fibrin glue however carries a theoretical possibility of transmission of HIV, hepatitis C virus, and prion-related diseases.[1]

Surgical repair

The following are the current indications for surgical repair:[11]

i. Bleb dysesthesia
ii. Large sweating bleb with hypotony maculopathy
iii. Frank bleb leak
iv. Blebitis.

The aim of bleb repair is not only closure of bleb leak or resolution of hypotony but also to preserve the bleb function. The reported overall success rates of bleb repair with various techniques were 80% to 86% at 1 year, which decreased to 50% at 5 years.[26-28] Table 4 enlists, in brief, the various techniques involved in surgical repair of a leaking bleb.

Table 4: A list of techniques of bleb repair that have been described

Procedure	Technique
Conjunctival advancement with or without excision and with or without conjunctival autograft[19]	A conjunctival relaxing incision is only indicated if the defect is large and the conjunctiva and tenon's capsule can be advanced without undue tension[20]
For defects <5 mm Conjunctival advancement Conjunctiva and tenon's are undermined at the limbus	In case of an excision, AMT can be used to cover the excised area, with or without conjunctival advancement
For defects >5 mm Pedicle graft or Autoconjunctival graft may be done	Addition of AMT is said to prevent subconjunctival fibrosis, thus allowing bleb functionality to be maintained[21]
Hinged scleral flap[22]	Sclera adjacent to the scleral flap is dissected in a lamella fashion to cover the area of scleral buttonhole/defect Relaxing incisions can be given to allow adequate mobility Base of the flap is oriented to include a vascular pedicle to maintain flap viability
Fistulectomy with scleral suturing[23]	
Scleral (pericardial) patch graft[24]	

AMT – Amniotic membrane transplantation

OVERFILTRATION

This occurs as a result of decreased outflow resistance when aqueous outflow exceeds the production. The identified risk factors for overfiltering blebs include (a) use of antimetabolites and (b) early laser suture lysis. It is characterized by an elevated bleb, shallow/well-formed AC, and a negative Seidel's test. The probable causes include (a) loose scleral flap sutures, (b) large scleral fistula, or (c) an exceptionally large area of filtering bleb. Table 5 highlights the management strategies involved.

Surgical revision of overfiltration is warranted, especially when associated with hypotony maculopathy. It involves the use of compression sutures, which were traditionally described by Palmberg, and were called Palmberg compression sutures.[29] Here, two longitudinal transconjunctival sutures are placed on either side of the scleral flap edge to provide adequate resistance to aqueous outflow, and thus limit the amount of aqueous egress. There have been modifications in this technique, one of which, as described by Yu *et al*.,[30] involves the use of two

Table 5: Management strategies of overfiltering bleb

Preventive measures	Medical management	Other measures
Protect conjunctiva from surgical trauma	Tapering dose of steroids	Firm patching for 2-3 days and cycloplegics
Tight scleral flap closure	Aqueous suppressants?	Deepening of AC with Balanced salt solution Sodium hyaluronate C3F8/large air bubble
	Prophylactic topical antibiotics	

AC – Anterior chamber

figure-of-eight transconjunctival sutures place horizontally over the scleral flap proximal to the limbus and the second one on the distal flap edge. The sutures could then be lysed sequentially, in cases of elevated IOP postoperatively, until an adequate IOP is achieved.

CILICHOROIDAL DETACHMENT

Imbalance between the fluid pressure in the eye and in the choroidal vasculature causes fluid to accumulate in the space between the choroid and the sclera, causing a detachment. Ciliochoroidal detachment, however, is more common after full-thickness surgery than trabeculectomy. The detachment is usually transient resolving with the administration of topical and systemic corticosteroids. However, presence of serum along with large protein molecules makes spontaneous resolution unlikely. Preoperative identification of high-risk eyes such as nanophthalmos and those with an elevated episcleral venous pressure, and subsequently taking adequate measures, helps in avoiding such complications. Indications for surgical drainage include (a) flat AC with lens cornea touch and (b) kissing choroidals.

CYCLODIALYSIS CLEFT

Cyclodialysis clefts are formed when the ciliary body becomes detached from the scleral spur. An abnormal free communication between the AC and the suprachoroidal space is formed thus increasing the uveoscleral flow, resulting in profound hypotony.[3] The cleft size, however, does not affect the degree of hypotony. They can be identified by gonioscopy; however, this can often be limited in soft eyes, in which case ultrasound biomicroscopy or anterior segment optical coherence tomography can be done.[3] Management strategies are described in Table 6.

IRIDOCYCLITIS: AQUEOUS SHUTDOWN

Decreased aqueous production occurs as a result of increased inflammatory response leading to the breakdown of blood-aqueous barrier, releasing pro-inflammatory mediators causing a ciliary body shock and shutdown. Hence, eyes predisposed to or presenting with substantial amount of postoperative inflammation, warrants an aggressive course of topical steroids.

RETINAL DETACHMENT

Although a very rare complication, serous RD and uveal effusion syndrome have been described posttrabeculectomy in nanophthalmic eyes with short axial length (14–17 mm).[31]

Table 6: Management strategies of cyclodialysis cleft

Medical measures	Surgical measures
Cycloplegics	Argon laser with Goldmann lens: To treat scleral region of small-sized clefts <1.5 clock h[3]
Topical atropine sulfate 1% is typically applied twice daily for as long as 6-8 (weeks)	Power 1.0-1.2 W to sclera, 0.3-0.7 W to choroid and ciliary body
	Spot size 200 μm
	Duration 0.5 s
Tapering steroids	Transscleral diode laser, or endolaser photocoagulation[3]
	Power 1500-2500 mW
	Duration 1500-2000 ms
	In two parallel rows over the cleft, 1.5 mm behind the limbus
	Transconjunctival cryotherapy[3]
	Used 3 mm behind the limbus to manually indent and close the cleft
	Using either a double or triple freeze-thaw sequence (−85°, for 30 s)
Recommended duration of cleft repair: within 3 months	

Direct cyclopexy is the best-studied intraocular approach to refractory clefts[3]

Table 7: Few of the less common causes of posttrabeculectomy hypotony

Cause	Remarks
Ocular ischemia	IOP is low in eyes with giant cell arteritis (GCA)
Chemical cyclodestruction	Inadvertent deeper penetration of subconjunctival antimetabolites
Pharmacological suppression	Inadvertently excessive usage of antiglaucoma medications
Photocoagulation or cryoablation of ciliary body	

IOP – Intraocular pressure, GCA – Giant cell arteritis

Other less common causes of postoperative hypotony are listed in Table 7.

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Integration of research with clinical skills for house surgeons

Dear Editor,

I agree with your editorial titled, "The science of research and the joy of discovery" published in the *Kerala Journal of Ophthalmology*, 2021, that intrinsic motivation and the excitement of discovery with new findings are major factors for research.[1] Medical education is a lifelong process that involves the development of pattern recognition and analytical, cognitive, and reasoning processes to appropriately interpret clinical signs and symptoms. The lack of development of these skills leads to faulty research, research waste, and a lot of research work that is accepted as oral presentations but does not stand up to the more intense scrutiny of publications.[2-4] House surgeons are at an interesting phase in their medical development as their transition to a more practical, pragmatic, hands-on application of the theory and concepts they have assimilated during the undergraduate course. I believe that the integration of research skills at this phase will help improve the clinical and decision-making skills of house surgeons and will help them when they move on to postgraduate residency programs.

One must overcome a multitude of hurdles on the way of successfully coming up with a research question, let alone completing one, as a house surgeon. The lack of appropriate knowledge about how to properly conduct a research study or about its positive effects on subsequent career paths and choices is a limitation. We have a brief exposure to research during our community medicine group project, following which research is often drowned among increased focus on achieving academic excellence alone. Our first, and in most instances, only exposure to undergraduate research is as a group project, and the technical know-hows, especially research logistics, ethical committee clearance formalities, data analysis largely remains unclear. A high score in the entrance examinations alone suffices, at least in the Indian medical scenario, to get admission into a postgraduate residency program; hence, research opportunities put forward by organizations such as ICMR go largely unnoticed. After this rather unsatisfactory initiation, our next exposure comes only when we must work on a postgraduate thesis, by then we limit ourselves only to small area of an assigned specialty and focus on the completion of the thesis rather than the quality of research. Hence, the undergraduate and house surgency period must be considered the ideal time to lay the foundation of clinical research when there are not any restrictions in terms of research topics or any time limits as such.

Funding is an essential prerequisite for research; unfortunately, national initiatives such as ICMR do not extend their research support to house surgeons. Limited access to research libraries and portals, data collection, and analysis software is also a major hindrance. Any successful research requires undivided attention and dedication. This might be nearly impossible for house surgeons, owing to untimely working hours, duties, and rapid rotation between services. In such a situation, the integration of research skills with the bedside clinical evaluation can help improve the decision-making skills and excite more interest in the house surgeon to pursue clinically meaningful research.

Every house surgeon must be encouraged to do a few research studies as part of the program. These could include a case report, a case series, or an original research study that can be completed in time. Co-opting house surgeons into ongoing studies and using the opportunity to integrate research and clinical skills are options that must be considered. Periodic classes or seminars and journal clubs must be arranged to help both undergraduate and postgraduate students understand how to integrate research methods and findings with clinical skills. More platforms should be set up for house surgeons to present completed studies, and official certificates are offered as an incentive and acknowledgment of research-related activities.

In conclusion, I think that medical education programs must actively consider a pathway with active mentoring that encourages house surgeons to develop as clinician-scientists.

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There are no conflicts of interest.

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Research in ophthalmology

Dear Sir,

It is with great interest that I read your Editorial in the last issue of KJO entitled, "The science of research and the joy of discovery."[1] The Editorial on the values of research is sure to ignite the spirits of the readers, especially the upcoming ophthalmologists. Ophthalmology, with its range of specialties and related investigations, provides a treasure house of data with myriad opportunities for research that is often unexplored.

There are so many impediments to research that currently exist. A major obstacle is a lack of motivation that is backed by the lack of proper orientation to the fruits of research. The lack of time for a clinician to balance the research work with a busy clinical practice poses a firewall for most. However, these hurdles will melt away once they are aware of the gifts that a properly conducted research offers and how it translates to one's clinical practice. High-quality clinical research always helps to substantiate our clinical knowledge and adds to our experience. When integrated with our clinical proficiency, it can enhance clinical decision-making and open the doors to a more creative and enriched clinical practice.[2,3]

Judicious utilization of time and resources to analyze the available data is a key to successful and productive research. I wish to share a few suggestions to promote research work in the institutions of the state. An initiative to include a research orientation package in the curriculum of the postgraduate resident programs of the state must be considered and will go a long way to provide the necessary motivation to those interested. Research-oriented and research-related programs may be incorporated into upcoming CME programs with the due importance they deserve. Institutions may provide incentives and funding for a dedicated research department in each of the institutes under the aegis of KSOS and KJO. The Annual Conference of KSOS may review the functioning of these research teams, and a session dedicated solely to this can help formulate specific guidelines and preferred practice patterns relevant to our state in key areas of interest. These guidelines may be published in the issues of KJO on a regular basis with updates as and when required. Key topics in areas with upcoming interest which need awareness among the practicing ophthalmologists must be addressed. Evidence-based guidelines on management must be promoted, if required so, in special issues. An example of such a topic will be the recent outbreak of orbital mucormycosis in the COVID-19 patients and those recovering from it.

I hope that the research mentorship program provides the stepping stones to research to the participants and moulds more "Evidence-oriented clinicians" in the future who incorporate the fruits of systematic reviews and meta-analyses into their clinical practice.

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