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Cover Story:

Upper row:
Fundus Image of LE showing the presence of sub retinal heme and oedema in the macula, AF image showing hypo autofluorescence in the macula & OCT Image showing subretinal hyperreflective material and intraretinal edema.
Lower row:
OCTA of LE showing branching vascular network with dense and frequent anastomosis around a central trunk of vessel in the avascular layer confirming the diagnosis of classic CNVM.

Contributed by:
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Editorial

The science of research and the joy of discovery

"Good research is not learned in books, but at the bench, like the crafts in the Middle Ages."

Christian de Duve[1]

Discovery requires research, and research implies exploring the unknown. Research conducted for the purpose of contributing toward science by the systematic collection, interpretation, and evaluation of data and that, too, in a planned manner is called scientific research.[2] The scientific method should be precise, replicable, and logical.

The scientific method was originally called the "Baconian method" as British philosopher Francis Bacon was the first to suggest that knowledge can only be derived from observations in the real world. From the actual observations, hidden concepts and patterns are identified. Research involves moving back and forth from these observations to a theoretical plane where the observations are converted to theories. This skill to transform observations into a hypothesis takes years to develop.

Intrinsic motivation is the fuel to sustain research. The joy of research in science derives from the excitement of discovery. As children, we start with a natural curiosity about everything around us. Unfortunately, as we grow up, this curiosity gets severely blunted by our responsibilities and environmental experiences. To destroy this natural curiosity or to attenuate the joy of discovery is the greatest disservice we do to the developing person. Why are so few of our capable students pursuing the level of education required for a successful research career? We have failed to promote the excitement and exhilaration of discovery.

It has been noted that medical trainees are essentially tested on their knowledge and skills base, but that this is inevitably incomplete at the point that they are qualified, there is thus a need for medical education to maintain curiosity, to drive lifelong learning.[3] In a study among clinicians at various stages of the neurosurgical career, the top three perceived barriers to conducting research were lack of time (78%), insufficient access to funding (58%), and lack of mentorship (49%). Despite these, more than 87% of participants were interested in formal academic roles with 58% willing to interrupt clinical training to pursue research opportunities.[4] Similarly in the UK, in a study conducted among geriatric medicine trainees, the majority (70%) indicated that they have no clear idea of a topic to research, 64% did not know how to develop an idea, and 62% indicated that they did not know how to get funding.[5]

So what needs to be done to regain that lost curiosity and the joyous feeling when we achieve some targets? Pattern recognition, analytical thinking, and similar abilities need to be stimulated. Research exposure increases understanding of clinical medicine; facilitates critical thinking and critical appraisal; improves prospects of successful application for postgraduate training, grants, and high-impact publications; develops teamwork skills; and increases exposure to the best clinical minds. However, we need to stress on the fact that beyond these job opportunities, research when it produces results gives a satisfaction and pride beyond mere words. Discoveries made especially in the health sector have a direct impact on improving the quality of life of so many other individuals.

The research mentor program provides an excellent opportunity for participants to experience how fulfilling, rewarding, and exciting research can be, and to expose them to the many facets of the research world. A good research mentor enables us to see the big picture of the research. The experience helps to bridge the gap between the tedium of research and the excitement of discovery and progress. With this in mind, *The Kerala Journal of Ophthalmology* starts the New Year with a new Research Mentorship Program. To ultimately share the message," Research is Exciting."

Sudha V

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Spectrum of uveitis in India



ABSTRACT

We look at the spectrum of uveitis in India before the year 2010 and after the year 2010, the changing patterns in uveitis over time, the probable factors for the changing patterns and newer uveitis entities in India.

Keywords: India, infections, patterns, spectrum of uveitis

INTRODUCTION

Uveitis is a sight-threatening disease and can arise from many causes. If not diagnosed and treated early and adequately it leads to irreversible blindness. Diagnosis is often challenging despite a better understanding of the pathogenesis and newer diagnostic modalities. Geographic factors play an important role in identifying the cause of uveitis. The pattern of uveitis in India differs considerably from that seen in the developed world.

In the 90s and early 2000, uveitis was a niche area in ophthalmology with only a handful of specialists in India and uveitis care was mainly restricted to tertiary care centers. However, in recent years, there has been an increase in the number of uveitis specialists all over India which is evident by the increasing number of articles on uveitis from the subcontinent. In this review, we aim to look at the spectrum of uveitis in India, the changing patterns over the years, probable factors resulting in the changing patterns and newer uveitis entities by a literature review.

MATERIALS AND METHODS

Literature search pertaining to the spectrum of uveitis in India published in PubMed, EMBASE, and MEDLINE was done. MESH terms like "Pattern of Uveitis"/"India," "Spectrum of Uveitis"/"India," "Uveitis"/"India," "Ocular Inflammation"/"India" were used. A manual search of references cited by retrieved articles for additional references were also done. Furthermore, authors conducted independent systemic review of the literature and retrieved the data. The data retrieved were separated into articles from India before the year 2010 and those after 2010 and the data analyzed.

RESULTS

Tables 1 and 2 provide the pattern of uveitis in India before and after years 2010 respectively.

DISCUSSION

Before 2010, uveitis care was restricted to tertiary referral

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Table 1: Pattern of uveitis in India from various studies before year 2010

Characteristics	Biswas *et al*., 1996 (South) (*n*=1273), *n* (%)	Singh *et al*.,[2] 2004 (North) (*n*=1233), *n* (%)	Rathinam *et al*.,[3] 2007 (South) (*n*=8759), *n* (%)	Das *et al*., 2009 (East) (*n*=308), *n* (%)
Anterior uveitis	39	49	57	47
Intermediate uveitis	17	16	10	13
Posterior uveitis	29	20	11	30
Panuveitis	15	15	22	10
Idiopathic	59.3	51.18	44.6	38.96
Specific etiology	40.7	48.82	55.4	61.04
Infection	11.9 Toxoplasmosis	29.7 Tuberculosis	30.7 Leptospirosis	18.83 Toxoplasmosis
Noninfection	28.8 VKH (3)	19.1 HLAB27 (7)	24.8 FHI (5) HLAB 27 (4) sarcoid (4)	45.13 VKH (10)

Table 2: Pattern of uveitis in India from various studies after year 2010

Characteristics	Venkatesh *et al*. (North) 2016 (*n*=980), *n* (%)	Dogra *et al*. (North) 2017 (*n*=1912), *n* (%)	Sabhapandit *et al*.[2] (South) 2016 (*n*=1123), *n* (%)	Borde *et al*. (Central) 2020 (*n*=210), *n* (%)	Bandyopadhyay *et al*. (East) 2019 (*n*=331), *n* (%)	Palsule *et al*. (West) 2017 (*n*=198), *n* (%)
Anterior uveitis	42.14	43.04	48.9	47.1	55.29	41.4
Intermediate uveitis	13.36	10.66	17.3	31.90	5.44	16.7
Posterior uveitis	16.83	24.58	20.5	11	23.87	20.7
Panuveitis	9.2	16.21	13.3	22	15.4	21.2
Idiopathic	77	39.44	38	48.09	43.5	49.5
Specific aetiology	23	60.56	61.4	51.91	56.5	50.5
Infections	9 Tuberculosis 60	33.42 Tuberculosis 22.9	31.1 Tuberculosis 19.6	25.71 Tuberculosis 46.29	- Tuberculosis 8.16	- Tuberculosis 52.73
Noninfectious	- HLAB27-7.5	27.14 HLAB27-9.46	30.3 FHI - 7.9	26.19 HLAB27 - (27.27)	- Behcets - 8.76	- HLAB27-53.33

centers due to the availability of only handful of uveitis specialists. There were only 4 major retrospective studies from India regarding the pattern of uveitis: 2 from south, 1 from north and 1 from the east.[1-4] Anterior uveitis was the most common type of uveitis across all 4 studies (39%–57%). In the late 90s and early 2000, >50% of uveitis cases were idiopathic. Infectious uveitis constituted 11.9%–30.7% in various studies. Toxoplasmosis was the most common type of infectious uveitis along with tuberculosis and leptospirosis. VKH was the most common type of noninfectious uveitis. Post 2010, there were more number of studies from all over India (2 from north, 1 each from south, central, western and eastern India).[5-10] This indicates that the number of uveitis specialists has increased across India and management is now no longer restricted to tertiary referral centers. Anterior uveitis was still the most common type of uveitis seen across all the studies (41.4%–55.29%). Interestingly, in contrast to earlier years, it was possible to identify the etiology in >50% of uveitis. Infectious cause constituted 9%–33.42% of cases of uveitis. Interestingly tuberculosis was the most common type of infection across all the studies (8.16%–60%). Among the noninfectious uveitis, HLAB27 anterior uveitis was most common.

Changing patterns

These studies at different timelines suggest changing patterns in uveitis. In recent years, in infectious uveitis, there has been a significant increase in the prevalence of ocular TB (22.5% vs. 0.64%, $P < 0.0001$). There has been an increasing trend of viral uveitis, especially a significant increase in viral retinitis (from 0.76% to 6.81%, $P < 0.05$). There has been declining trend in toxoplasmosis ($P = 0.0545$) and cytomegalovirus (CMV) retinitis. In the noninfectious uveitis, there has been an increase in HLAB27 positivity (29.83% vs14.5%; $P < 0.05$) and ocular sarcoidosis.[11]

One of the important aspects in the changing pattern of uveitis is the possibility to establish the etiology in >50% of cases. This is probably due to the availability of newer diagnostic technologies in India. This includes ocular imaging (ICG, Spectral OCT, OCT-angiography, adaptive optics, etc.), polymerase chain reaction (PCR), availability of high resolution computed tomography scans and endobronchial ultrasound-guided transbronchial lymph node aspirations to get a definitive diagnosis. Ocular imaging has definitely helped us to understand the level of pathology and hence, the pathogenesis better. PCR has

played a very important role in infectious uveitis, especially the identification of viral etiology, especially CMV and tuberculosis.[12-14] Chest X-ray is more often replaced by HRCT thorax[15] in many cases of uveitis, especially granulomatous uveitis and availability of EBUS-TBNA have helped us to achieve a biopsy-proven diagnosis in many of our cases of tuberculosis or sarcoidosis.[16]

Multicentric studies across India have set diagnostic criteria including recognition of clinical parameters/phenotypes for the diagnosis of ocular tuberculosis and ocular sarcoidosis. Noted among these are Collaborative ocular tuberculosis[17] and the ocular sarcoidosis[18] studies. In addition, individual studies from the subcontinent have contributed significantly to identifying clinical predictors and prognostic factors for TB associated uveitis.[19-21] If we look at the literature before 2010, it is noted that many cases of serpiginous choroiditis were placed in the noninfectious group and were treated with immunosuppression. However, this clinical phenotype of serpiginous like choroiditis is now increasingly recognized to be presumed ocular tuberculosis in high Tb endemic countries like ours and are now treated with antitubercular therapy. Similarly, Eales disease, once thought to be idiopathic, is increasingly recognized to be associated with tubercular etiology especially in high TB endemic countries like ours.[22] We believe that the availability of these newer diagnostic modalities and multicentre studies have played an important role in identifying cases of ocular tuberculosis and thus the most common cause of infectious uveitis across India. Sarcoidosis was once considered a disease of the developed world. In recent years, there have been increasing reports of sarcoidosis from our part of the world. It is now being considered routinely in the differential diagnosis of both ocular and nonocular diseases. The role of mycobacterium tuberculosis in the development of sarcoid is being increasingly investigated due to the clinical, radiological and histopathologic similarities with tuberculosis. This is one of the reasons to differentiate between ocular tuberculosis and ocular sarcoidosis in high TB endemic countries like ours. The multicentre study from India on the diagnostic markers in ocular sarcoidosis in a high TB endemic population is useful in differentiating the 2 conditions to some extent.[18]

Another important factor in identifying the etiology is the multidisciplinary approach which is being followed in recent years. Over the years, we have learnt a lot from our colleagues in rheumatology, pulmonary medicine, dermatology, etc., and the availability of their expertise and newer diagnostics in their respective fields have helped us in identifying the cause of uveitis. One of the significant changes has been in juvenile idiopathic arthritis (JIA). In earlier years, children with JIA with uveitis presented with sequelae such as band-shaped keratopathy, occlusio and seclusio pupillae, and glaucoma as they presented very late in the disease course to an ophthalmologist. However, in recent years, children are being increasingly referred for an ophthalmic evaluation at the time of detection of JIA and hence seldom see such bad sequelae. Blau syndrome was thought to be very rare in India. However, due to the recent availability of genetic testing, there have been increasing reports of blau syndrome from our part of the world.[23]

Third, the availability of newer drugs now to treat ocular inflammation. We have come a long way from steroids to immune suppressives and now to targeted therapy in the form of biologics. Our lower threshold for immunosuppression and targeted therapy has led to better control of inflammation and better prognosis in our cases. On the flip side, we are seeing more cases of drug-induced uveitis in recent times.[24] Local therapy such as implants and biosimilars have reduced the cost of treatment significantly.

Fourthly, there has been an impact of national disease control programs on the changing patterns of uveitis. Noted among this is the national aids control programme. The NACO 2015 report[25] shows a declining trend in estimated newer HIV infections and AIDS-related deaths in India [Figure 1]. This is possible due to the easy availability of free antiretroviral therapy. The National tuberculosis control program is another national wide program rolled out in recent years to eradicate tuberculosis.

Newer uveitis entities

In recent times, we have seen the resurgence of older diseases such as syphilis in non-HIV patients. The RPR titers are higher in patients with HIV than in non-HIV patients. We have also had epidemics of chikungunya, dengue, and West Nile fever. These have led us to see newer uveitis patterns such as multifocal retinitis. Interestingly all of them follow a similar pattern and are generally associated with a favorable prognosis unless associated with vascular occlusions. New terminology has been coined to describe this pattern of retinitis called "post fever retinitis."[26,27] Although CMV retinitis in HIV has declined considerably, we are seeing an increase in the incidence of CMV retinitis in non-HIV cases Eg; post intravitreal steroid injections and implants. Unlike the CMV retinitis in HIV, the CMV retinitis in non-HIV are refractory to treatment requiring multiple injections of ganciclovir and progression to neovascularisation due to associated vasculopathy and ischemia. Rickettsia retinitis is a newer uveitis entity especially in south India.[28] It may be associated with vascular occlusions. Rickettsia infections

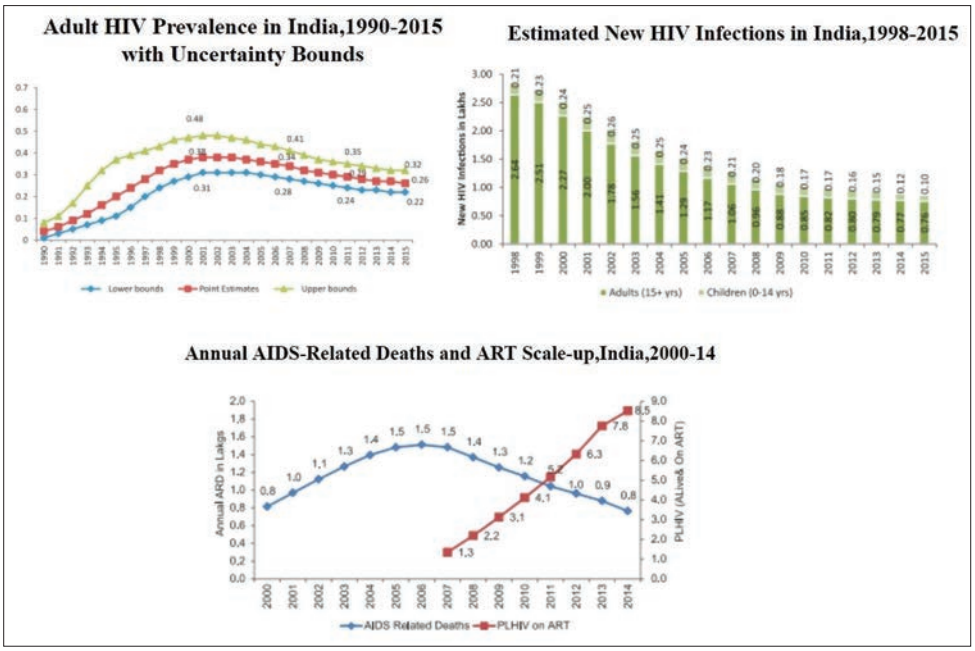


Figure 1: Photograph showing decreasing trend of new HIV infections in India and increased use of antiretroviral therapy. NACO 2015 report

especially in children with a history of pyrexia of unknown origin are increasingly more common. They respond very well to doxycycline and cephalosporins. Lyme disease was never a part of differential diagnosis in India. Recently there has been an increasing number of case reports of Lyme disease in India. In a recent study, it was noted that there is a high seroprevalence (19.9%) of borrelia burgdorferi infection in the Western ghats region in south India. This was also confirmed with western blot (15.6% positivity).[29] Incidentally, another study confirmed the presence of Ixodes ticks in these regions. There have also been case reports and series of neuroretinitis in patients from this region responding well to doxycycline. Thus any patient hailing with characteristic symptoms and signs from these regions, Lyme disease must be kept as a differential diagnosis even in a country like India. Due to the global coronavirus (SARS-CoV-2) outbreak, reports of Kawasaki disease, increase in IOP, retinal vascular occlusions, hyperreflective lesions in the inner retina and papillomacular bundle, panuveitis, and optic neuritis have been described.[30]

So what has been the real change in our practice of management of uveitis? It is our approach to these cases. Uveitis is no longer a niche area in ophthalmology. Thanks to efficient dissemination of information in the form of study groups, newsletters, conducting CMEs, training at both national and international levels, we have more number of ophthalmologists treating uveitis cases across India. There is also an increased awareness of varying aetiologies and presentations (from infective to autoimmune). Regular updates in newer developments in pathogenesis, diagnostics, and therapeutics and rapid progress in diagnostics (ophthalmology and nonophthalmology) and therapeutics have played an important role in uveitis care. A multidisciplinary approach, involving working closely with other departments in internal medicine have helped us to work as a team resulting in better uveitis care and hence better prognosis for our uveitis patients.

CONCLUSION

The spectrum of uveitis in India is changing rapidly due to global migration, increasing uveitis specialists in India, the availability of improved diagnostics and therapeutics, and utilizing a multidisciplinary approach. These have resulted in improved uveitis care in India and a better prognosis our uveitis patients.

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Glaucoma in pregnancy: An update and practical guide

ABSTRACT

Lack of clear guidelines and understanding makes management of glaucoma during pregnancy a major challenge. The treatment should be balanced in such a way that it is safe for the mother and the growing fetus while maintaining the intraocular pressure control and stability of glaucoma.

Keywords: Glaucoma, laser, pregnancy, selective laser trabeculoplasty, trabeculectomy

INTRODUCTION

Pregnant women may have preexisting glaucoma from childhood that may need monitoring.[1] Managing glaucoma in pregnant women is a challenge for both the patient and the treating doctor.[2] The intraocular pressure (IOP) is known to reduce linearly as pregnancy advances.[3,4] However, close to one-third of the women have elevated IOP,[5] and those with preexisting glaucoma may worsen needing additional medical treatment, laser, or surgery.[6]

The management benefits have to be weighed assessing the benefits of treatment versus the potential risks for both mother and the fetus.

The paucity of literature due to ethical and legal constraints in conducting clinical trials on pregnant women leaves us with no evidence-based guidelines for the management of glaucoma in pregnancy. In this article, we discuss the practical considerations in medical management, laser therapy, and surgical intervention for glaucoma in pregnant women.

MEDICAL MANAGEMENT

According to the United States Food and Drug Administration (FDA), none of the antiglaucoma medications (AGMs) are considered safe in pregnancy.

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Table 1 shows the FDA classification of AGMs based on the safety profile of the drugs.[1]

The only antiglaucoma medication available in Category B is topical alpha agonist.[1] Category C drugs include topical beta-blockers, prostaglandin analogs, topical and oral carbonic anhydrase inhibitors, and parasympathomimetics.

AGMs have potential side effects at various stages of pregnancy. The risks include teratogenicity in the first trimester, premature labor in the second and third trimester, and potential toxicity to the new born due to the secretion of the drug through the breast milk during postpartum and lactation. Each class of medication has special concerns for usage during pregnancy and lactation.[1]

Table 2 shows the recommended class of AGMs according to the trimester of pregnancy.

Beta-blockers

Oral beta-blockers are classified as Category C drugs;[1] however, beta-blockers are used to treat hypertension during pregnancy.[7]

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Table 1: The Food and Drug Administration classification of antiglaucoma medications based on the safety profile of the drugs[1]

Category of the drug	Evidence
Category A	Medications that have strong evidence of safety, based on human studies
Category B	Medications that have varying human and animal data. For example, a drug is graded as Class B if animal studies showed some harm but human studies indicated safety, or if animal studies have shown safety but no human studies were available
Category C	Describes medications that showed side effects in animal models, or where inadequate animal and human studies were available
Category D	Medications with established risk to the fetus in animal studies
Category X	Drugs that show strong evidence of birth defects

Table 2: The recommended class of antiglaucoma medications according to the trimester of pregnancy

	First trimester	Second trimester	Late pregnancy and lactation
The first line of medications	Alpha-agonist	Alpha-agonist	Parasympathomimetic Topical carbonic anhydrase inhibitor
The second line of medications	Topical carbonic anhydrase inhibitor Topical beta-blocker	Topical carbonic anhydrase inhibitor Topical beta-blocker Prostaglandin analog Parasympathomimetic Oral carbonic anhydrase inhibitor	Prostaglandin analog Topical beta-blocker Oral carbonic anhydrase inhibitor
Contraindicated medications	Oral carbonic anhydrase inhibitor Prostaglandin analog Parasympathomimetic		Alpha-agonist

Topical beta-blocker may cross the placenta and cause fetal bradycardia, and beta-blockers may cause neonatal respiratory distress and apnea due to secretion into breast milk.[1]

Alpha agonists[1]

Brimonidine is a Category B medication. Although well tolerated, its use should be discontinued close to labor and during lactation due to its potential side effects of central nervous system depression and apnea in infants.

Prostaglandin Analogues[1]

Prostaglandin Analogues (PGAs) are Category C drugs shown to be associated with miscarriages in animal studies. It can stimulate uterine contraction producing preterm labor; however, it is unclear whether ophthalmic dosage can induce this side effect. Given this theoretical risk of premature labor, PGAs are not used as the first line of medication during pregnancy.

Carbonic anhydrase inhibitors

Topical medications are classified under Category C. Animal studies have shown that both brinzolamide and dorzolamide cause teratogenicity and low birth weight.[1] There is no convincing evidence for the adverse effect of acetazolamide in pregnancy. However in early pregnancy, <13 weeks of gestation using oral carbonic anhydrase inhibitor (CAI) is not recommended but could be used with caution in the second and third trimester.[8,9] The use of oral CAI in late pregnancy needs close monitoring as it can cause neonatal electrolyte imbalance and metabolic acidosis.[1,2,10]

Cholinergic medications

There is no known association between the use of topical pilocarpine and congenital abnormalities; however, few instances of hyperthermia and seizures in neonates were recorded and hence may be avoided during postpartum and lactation.[1,10]

Other Drugs

Rho-associated protein kinase inhibitors when used systemically may cause excessive vasodepressor action. Although topical use of these medications minimizes the undesirable adverse effects, there are concerns about the effects of long-term usage and tolerance to the drug.[11,12] There is no published evidence on its use in pregnant women.

Drainage of the drug through the nasolacrimal duct, lack of ocular metabolism, and bypassing hepatic enzymatic metabolism causes systemic absorption of drugs[13] and exposes the fetus to the side effects of AGMs.[1,2]

Simple techniques such as punctal occlusion and eyelid closure can reduce systemic absorption.[1] Medical management requires a fine balance between the risk of vision loss to the mother and the side effects of AGMs on the fetus.[1] Hence, pregnant women should be prescribed minimum medications and only when necessary.

LASER THERAPY

Selective laser trabeculoplasty is a useful alternative to reduce the number or need for AGMs and possibly defer surgery in pregnant women.[14,15] However, inability to perform laser trabeculoplasty in dysgenetic angles, lower efficacy in young patients, delayed onset of IOP reduction,[1] and compromised

long-term IOP control limits its use.[16] There is scant literature on the use of micropulse or diode cyclophotocoagulation to control IOP during pregnancy.[17] Given the SHORT TIME FRAME OF PREGNANCY, trabeculoplasty should be considered whenever feasible.[2]

GLAUCOMA SURGERY

Surgery is best avoided during pregnancy. However, IOP can increase and preexisting glaucoma can worsen despite medical and laser treatment.[2,5,18] Failure of conservative management combined with disease progression makes surgical intervention inevitable.[19] Glaucoma surgery during pregnancy has serious risks. Challenges are related to preoperative planning, anesthetic concerns, intraoperative modifications, and postoperative management.

Altered maternal physiology predisposes pregnant women to hypoxia, hypercapnia, and systemic hypotension, which exposes both mother and fetus to the risk of anesthesia, more so with general anesthesia.[1] Additional challenges include difficult airway management because of gastroesophageal reflux and increased risk of aspiration. Placental transfer of anesthetic agents such as narcotics, paralyzing agents, and inhalational agents can cause fetal cardiovascular and central nervous system depression.[18] There are no well-controlled human studies on the teratogenic effects;[8] however, reports show an increased incidence of low birth weight and neural tube defects with exposure to general anesthesia in the first trimester.[9] Local anesthetics used in current ophthalmic surgeries have not shown teratogenic effects in humans and are considered relatively safe in pregnancy.[19] However, fetal bradycardia was noted with bupivacaine but not with lidocaine.[20] Topical anesthesia augmented with subconjunctival and anterior sub-Tenon's anesthesia causes less systemic absorption of anesthetic drugs,[21] and hence, it is advisable to limit the drugs to the minimum required dose for effective analgesia.

Supine position in the second and third trimester can cause profound systemic hypotension as the gravid uterus tends to compress the aorta and vena cava. It is advisable to rotate patients' hip, abdomen, and thighs to the left lateral position while maintaining a normal head position for surgery. As chances of gastroesophageal reflux are high, the full stomach should be avoided during surgery.[1,19] It is advisable to defer surgery till the second trimester to prevent potential hazards of teratogenic anesthetic agents on the fetus.[22] However, the risk of surgery also increases substantially as the fetus grows in the second and third trimester.[1]

Although there are no studies that report the teratogenic effects of mitomycin C or 5 fluorouracil on the human fetus, the mechanism of action of the drug strongly suggests a potential hazard of teratogenicity, and hence, it is safer to avoid antimetabolites during pregnancy.[1,22,23] However, because of a high risk of bleb scarring in young patients, a subconjunctival, biodegradable, collagen (Ologen) implant can be used as an adjunct to modulate wound healing and prevent subconjunctival fibrosis.[24]

Topical antibiotics can be used judiciously in the postoperative period.

A study on fluoroquinolones (a Category C drug by FDA) shows no risk of congenital anomalies.[20] Category D drugs, tetracyclines, and aminoglycosides are considered unsafe in pregnancy. Topical corticosteroids are the routine postoperative medications following glaucoma surgery. Given the strong neeed to use steroids and the absence of clear complications associated with topical steroids, it can be used in pregnant women.[1]

Homatropine hydrochloride 2% eye drops and Atropine sulfate 1% eye drop can be used, as the ophthalmic dosage of these drugs is less likely to affect the fetus. However, homatropine might be a better option, as atropine may cause fetal bradycardia.[8]

All topical medications should be prescribed with punctal occlusion and eyelid closure to reduce systemic absorption. Patients should be advised to avoid blinking immediately after instillation of eye drops as blinking can activate the lacrimal pump and increase systemic absorption.[1,20] However, utmost care and caution should be exercised during punctal occlusion in the early postoperative period, avoiding additional pressure on the eyeball, and taking appropriate hygienic precautions.

SUMMARY

Management of elevated IOP during pregnancy differs based on the trimester of pregnancy, the severity of the disease, and risk versus benefit of treatment. Although IOP is known to decrease during pregnancy, some patients develop uncontrolled IOP not amenable to medical treatment and may need laser trabeculoplasty or surgery. If surgery is indicated, it might be safer to perform the same during the second trimester.

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Asymptomatic iris cyst encroaching anterior chamber angle

A 70-year-old male presented with complaints of diminution of vision in both eyes (OU) for the past 6 months. Best-corrected visual acuity was 20/80 OU. Intraocular pressure was 16 mmHg and 14 mmHg in the right eye (oculus dextrus) and left eye (oculus sinister), respectively. Anterior segment examination in OD revealed normal anterior chamber, primary mid zonal iris pigment epithelial (IPE) cyst[1] extending from 7 to 10 o'clock and grade 2 nuclear sclerotic cataract [Figure 1a]. Fundoscopy revealed 0.4:1 Cup disc ratio and rest was within normal limits. Gonioscopy in OD revealed open angles with iris cyst encroaching the nasal, superior, and inferior angle [Figure 1b-d]. There was no ectropion, corectopia, any feeder, or intrinsic blood vessels as often observed with melanoma.[2] The patient was diagnosed as iris cyst with grade 2 nuclear sclerotic cataract. The patient was advised ultrasound biomicroscopy (UBM) to rule out ciliary body involvement and follow-up with reports. On UBM, IPE cyst shows a very thin wall with absent reflectivity while melanoma is centrally dense with vascular pulsations, and arises from the uveal structures.[3] Meticulous examination with close follow-up is mandatory as IPE cyst can progressively infiltrate anterior chamber angle and manifest with acute angle closure.[4,5]

Clinical sign – Primary mid zonal IPE cyst extending with grade 2 nuclear sclerotic cataract.

Seen in[1]

1. Primary cysts-idiopathic-iris pigment epithelium cysts, iris stromal cysts
2. Secondary cysts-epithelial downgrowth-postsurgical, posttraumatic, cysts secondary to intraocular tumors-iris melanoma, medulloepithelioma
3. Medication-induced-miotics (phospholine iodide), prostaglandins
4. Cysticercosis infection.

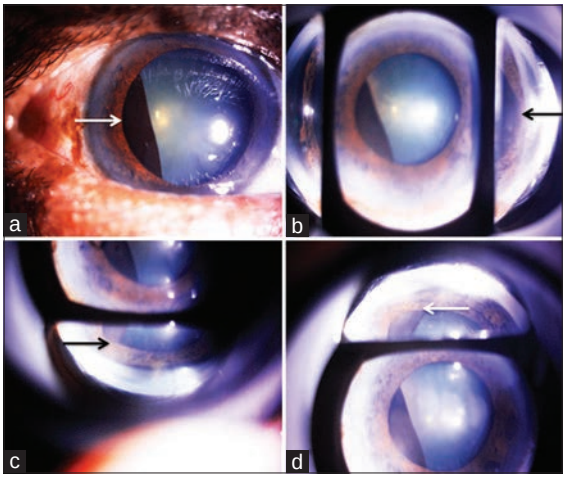


Figure 1: Image depicting (a) primary mid zonal iris pigment epithelial cyst extending from 7 to 10 o'clock (white arrowhead) and grade 2 nuclear sclerotic cataract (b) gonioscopic image of the nasal angle of the right eye depicting infiltration of iris cyst in anterior chamber angle (black arrowhead) (c) gonioscopic image of the superior angle of the same eye depicting iris cyst encroaching the angle with abutting ciliary body band (black arrowhead) (d) gonioscopic image of the inferior angle of the same eye depicting iris cyst approaching the angle (white arrowhead)

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Described by – Mackenzie diagnosed the first iris cyst in 1830.[3]

Why it occurs – The pathogenesis of primary iris cysts is not entirely understood, and proposed mechanisms are controversial. IPE cysts are thought to be remnants of the marginal sinus of the iris that have not been obliterated. The presence of goblet cells in iris stromal cysts suggest that they are formed by entrapped surface ectoderm tissue likely during formation of the lens vesicle (4th week of embryogenesis).[1,3]

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 understands that his name 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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Major Review

Amblyopia – An update

ABSTRACT

Amblyopia is the most common cause for preventable monocular visual loss in children. Visual system at birth is at a stage of dramatic developmental neural plasticity. Abnormal visual impulses from eyes (e.g., visual deprivation and refractive error) can affect normal anatomical and functional organization of the system. Abnormal cortical changes thus produced can be reversed if proper treatment is instituted during this time. This so-called critical period was thought to extend from birth to 7–8 years. However, now, it is understood that cortical plasticity though reduced may extend up to 6th decade of life and this accounts for increased interest in the management of adult amblyopia. Early detection and instituting treatment on detection are important for achieving better outcomes. Classical amblyopia treatment modalities include optical correction of significant refractive errors, occlusion therapy and penalization. Pharmacologic therapy, binocular therapy, and liquid crystal display eyeglasses are the newer treatment options. This review gives a simplified update of amblyopia including simplified pathophysiological concept in different types of amblyopia which will be useful to the clinician. Recent treatment options available for treatment including that in adult amblyopia are also discussed. Literature search using Google scholar, PubMed with a combination of words appropriate to this article was done and relevant articles were reviewed.

Keywords: Amblyopia, occlusion therapy, orthoptic therapy, penalization, refractive correction

INTRODUCTION

Amblyopia or "Dullness of vision" is the most common cause for visual loss in children that originates in childhood and demands early intervention. Defined as unilateral or occasionally bilateral reduction in best-corrected visual acuity (VA) which occurs in otherwise normal eye or eye with structural abnormality in which decrease in vision cannot be attributed solely to the abnormality.[1]

Clinically, amblyopia is diagnosed by a difference in VA between the eyes of two lines or more by any VA table, or VA worse than 20/30 with best refractive correction.[2] Amblyopia is usually unilateral and rarely bilateral. The prevalence of amblyopia varies in different parts of the world. In India, it has been documented to be between 1% and 6%.[3,4] Amblyopia is more than four times as common in infants who are premature, small for gestational age or who have a first-degree relative with amblyopia.[5]

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PATHOPHYSIOLOGY

Visual system is not fully developed at birth and is in a stage of dramatic developmental neural plasticity. For proper development of visual functions, three fundamental conditions are required-adequate stimuli from both eyes, ocular parallelism, and integrity of visual pathways. At this stage, abnormal visual inputs from the eyes (e.g., visual deprivation, refractive error) can affect normal anatomical and functional organization of the system. Asymmetry of visual inputs from right and left eye make the visual cortex prefer one eye over the other, leading to a number of functional deficiencies in the eye, altered visual function like decreased

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vernier acuity, and impaired contrast sensitivity, particularly to detect high spatial frequency stimuli and impaired motor signs like hand-eye coordination and spatial localization. Abnormal cortical changes thus produced can be reversed if prompt treatment is instituted during this time. This so called "critical period" continues postnatally till age of 7 years. After this cortical plasticity decreases but is never lost till one is in the 6th decade.[6] This is the basis of increased interest in the management of adult amblyopia. Maturation of visual system is completed by inhibitory gamma-aminobutyric acid genic interneurons in layer 2 and 3 of V_1.[7] The inhibition of these interneurons is thought to prolong plasticity.[8]

Understanding pathophysiology can be considered under two headings:

1. Normal organization of retino-geniculo-cortical pathway

There are two major groups of ganglion cells in retina responsible for processing light energy into electrical impulses. They are Parvocellular (P cells) involved in VA, fine stereopsis and color vision and magnocellular (M cells) cells in gross stereopsis and movement recognition.[9] P cells have higher representation in sensory cortex areas. After partial decussation in chiasma nerve fibers enter lateral geniculate body (LGB). Here, fibers from right and left eyes are distinctly separate and parvocellular and magnocellular fibers end in different layers. Mono-ocular separation of corresponding retinal areas continues through lateral geniculate laminae into striate cortex V_1 where geniculate axon terminals from right and left eyes are segregated into a system of alternating parallel stripes called ocular dominance columns (ODC). From there, paired right and left monocular cells finally converge in first binocular cells in layers 2, 3, 4α, 4Cβ of V_1. Binocular vision and motor fusion are made possible by horizontal connections from monocular columns to be shared[10] [Figure 1].

2. Corticogeniculate changes occurring in common types of amblyopia.

STIMULUS DEPRIVATION AMBLYOPIA

Usually seen associated with conditions such as congenital cataract and ptosis. Abnormal visual experience strongly affects retino-geniculate-cortical pathway. The two eyes compete for synaptic contacts in cortex. Affected eye loses connections already formed with post synaptic cortical targets and excessive pruning of terminal axons of geniculate cells driven by the affected eye. Hubel and Wiesel in their classical studies in macaque monkeys showed that when one eye was sutured close soon after birth lead to radically

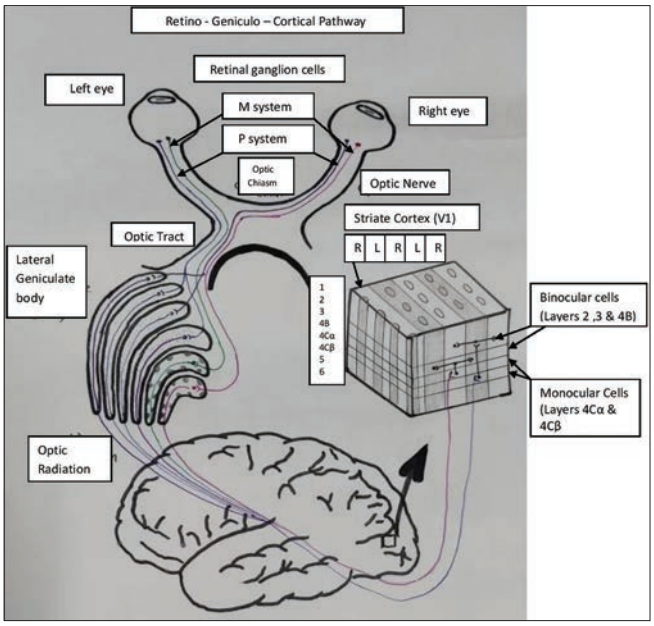


Figure 1: Retino-geniculo-cortical pathway

narrowed ODC in that side [Figure 2] and shrinkage of lateral geniculate laminae required to sustain reduced arbor of cells in 4c of amblyopic eye. Whereas ODC of other eye was found to expand and enlargement of LGB cells occur in normal side. In visual cortex number of synaptic connections continue to increase until 6 months of age and gradually fall back to normal adult levels.[11] Maximum interconnections are formed between parvocellular fibers and they also are more susceptible to visual deprivation. But, during this critical period, reopening of sutured eye and closure of other eye will cause the ODC of initially closed to become normal. This did not happen if eye was reopened after critical period. Little change was observed in LGB laminae in the affected eye if eye was closed after 2 months indicating a second sensitive period where changes occurring are different.[12] Profound cortical anatomical changes and greatest impact of all visual functions is seen in this type of amblyopia.

ANISOMETROPIC AMBLYOPIA

Anisometropic amblyopia can be associated with any type of refractive error especially with hypermetropia where a clear defined image is never obtained. Difference in refractive error between the two eyes to cause amblyopia varies with the type of refractive error. There should be at least a difference of 1 diopter between the two eyes.[13] Although anisometropia may be considered as a moderate form of stimulus deprivation amblyopia anatomical and functional changes found are different. Critical period in this amblyopia occurs much later than strabismic type and requires longer periods of optical blur. It is seen that proportion of cortical neurons responding to affected eye are much smaller. Optical defocus

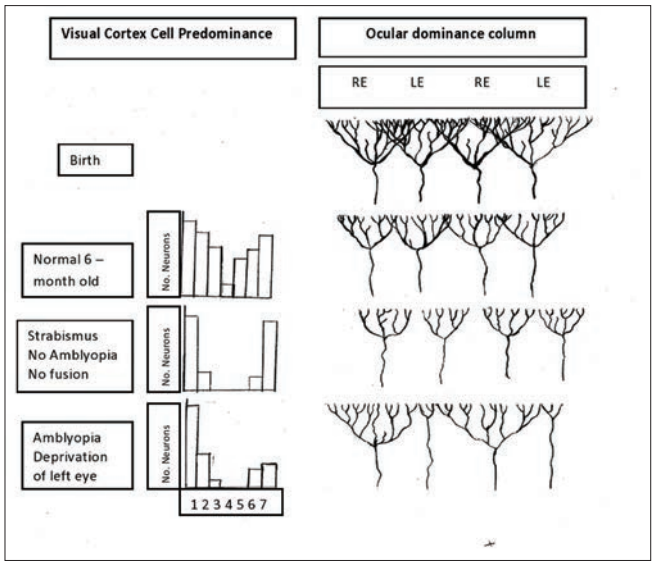


Figure 2: Ocular dominance columns

causes the cortical neurons driven by the defocused eye to be less sensitive to higher spatial frequencies because they are most affected by blur and send out weaker signals.[14,15] There is little narrowing of ODC and cell shrinkage of parvocellular pathway.

In this condition, congruent images are received by the brain despite difference in output from both eyes. Suppression is foveal and peripheral retinae continue to fuse images.[16,17] Anisometropic amblyopia leads to significant visual deficits compatible with loss of contrast sensitivity of all spatial frequencies with relative sparing of binocular vision.

STRABISMIC AMBLYOPIA

Strabismic amblyopia occurs in a child with unilateral squint and more so in esotropes. Deviation of one eye causes loss of parallelism. Fovea of the fixing eye and extra foveal point of deviating eye are stimulated (noncorresponding points). Uncorrelated images reaching brain results in inhibition of retino cortical path way from the deviating eye. There occurs active suppression of affected eye, loss of retinal correspondence and cellular interactions are altered. Studies done in monkeys showed that parvocellular recipient layer to be most affected with loss of binocular cells. ODC remain structured even in case of moderate amblyopia and only in deep amblyopia are there reports of alteration of ODC.[18] Strabismus cause a loss of connectivity to spatial information pathways causing defects in integration of contour and shapes. This affects numerous discriminating visual tasks including VA, vernier VA and crowding.[19-21] In strabismic amblyopia, there is no binocular facilitation of any stimulus and suppression is constant and strong. Suppression is also found in the fovea of the normal eye when amblyopic eye is fixing showing that lost VA is not related solely to suppression. Thus, it is suppression that leads to amblyopia in an individual who has strabismus and not vice versa, because the inactivity of the system may interfere with the process of synaptic development.[22] Loss of binocularity also affects stereopsis but contrast sensitivity is less affected than in other types of amblyopia with changes mainly to high spatial frequencies.[23-25] Strabismic amblyopia has major impact on VA and binocularity and contrast sensitivity is relatively spared.

NEWER UNDERSTANDING IN PATHOPHYSIOLOGY IN AMBLYOPIA

The presence of higher order cortical defects such as deficiency in movement integration, perception of shape and global contour, crowding phenomenon and visual decision making made researchers suspect involvement of extra striate areas in amblyopic patient. Investigations such as positron emission tomography, magneto encephalography, functional magnetic resonance imaging were used to demonstrate involvement of V1 and also involvement of ventral $V_{2,4,8}$ and dorsal median temporal area MT(V5). Studies with fMRI are also confirming different impacts on visual cortex related to different types of amblyopia. Recent findings suggest a more profound disorganization of the cortical arrangement in patients with strabismic amblyopia, in which the interhemispheric asymmetry for parvo- and magnocellular input processing was lost, whereas normal cortical asymmetry was present in those with anisometropic amblyopia.[26-28]

MANAGEMENT OF AMBLYOPIA

Comprehensive work up of the patient including relevant history helps in accurate diagnosis and suitable treatment. Minimum work up as per AIOS guidelines[29] include:

1. VA both eyes (in the case the child can read)
2. Fixation of either eye to be noted and recorded
3. Glow of each eye to look for gross refractive error and media clarity
4. Worth four dot test
5. Cover and uncover tests to rule out strabismus
6. Bruckner's red reflex test
7. Baglioni's striated glass test
8. Fundus examination.

The goal of treatment is equal VA between the two eyes, which may or may not be achieved in all cases. The treatment should be based on the child's age, VA, and compliance and response to previous treatment as well as the child's physical, social, and psychological status.

Principles of amblyopia management:

1. Eliminate the cause for amblyopia
2. Correct any refractive error
3. Force the use of amblyopic eye by limiting the use of normal eye.

PREVENTIVE SCREENING

This is the most important part of the treatment strategy. Success rates of amblyopia treatment decline with increasing age.[30,31] The American Association of Ophthalmologists suggests visual screening of all children at least once by 3–5 years.[32] Screening improves vision outcomes, decreasing the prevalence of amblyopia by as much as 60%. A study by Pediatric Eye Disease Investigator Group of treatment of moderate strabismic and/or anisometropic amblyopia demonstrated that the VA of the amblyopic eye improved to 20/30 or better 6 months after initiating treatment in approximately three-quarters of children under 7 years of age.[33] When amblyopia is present, it appears that the potential for successful treatment is greatest in young children, although improvement in VA can reasonably be expected in older children and teenagers.[34-36] However, treatment should be offered to all regardless of age. Primary care providers may be equipped with novel technologies, such as instrument-based devices (vision screeners) like to diagnose amblyopia in the early stages.[37] Recent studies in India with the Spot PS vision screener showed that it can be used to detect amblyogenic factors in children younger than 5 years of age keeping its limitations in consideration.[38]

Factors affecting treatment success

Prognosis for attaining normal vision in an amblyopic eye depends on many factors, including the age of onset; the cause, severity, and duration of amblyopia; the history of and response to previous treatment;[30] adherence to treatment recommendations and coexisting conditions.

Treatment options include

Refractive correction

In children of age 0–17 years with amblyopia initial treatment is correction of refractive error.[30,34,39] Cycloplegic refraction and adequate optical correction given in all patients [Figure 3]. There occurs improvement in 77% and resolves in 25% of patients (amblyopia treatment study [ATS] 5).



Figure 3: Refractive correction addressing squint and amblyopia

Occlusion therapy

Occlusion therapy is based on principle of creating new neural connections through the property of neural plasticity of brain and retrains the visual system to use both eyes equally. In this method, the "stronger" eye is patched so that the "weaker" eye is forced to break any suppression and use its visual pathway.

a. Whom to patch: Patching[33,40,41] is initiated for children in whom amblyopia persists after treatment for 4 months with eye glasses alone. This treatment is most effective with younger children under 7 years of age. Significant improvement in vision with patching can be achieved in children up to 13 years of age, although they may require a higher dose of patching, the rate of response to treatment may be slower, and the extent of recovery may be less complete. Patching should be considered for older children and teenagers, particularly if they have not previously been treated[30]
b. How much to patch: The ATS found that 6 h of prescribed daily patching produces an improvement in VA that is similar in magnitude to full time occlusion therapy prescribed for treating severe amblyopia (20/100–20/400) in children under 7 years of age.[42] In children who have moderate amblyopia (20/40–20/80), initial therapy of 2 h of prescribed daily patching produces an improvement in VA that is similar in magnitude to the improvement produced by 6 h of daily patching.[40] Higher hours of patching were associated with worse compliance: Only 6% of patients with higher hours of patching complied for the prescribed time.[43] The treatment benefit achieved by the patching appears stable through at least 15 years of age. Occlusion amblyopia and appearance of a constant deviation are important complications of this treatment
c. Patching continued till equal or optimum VA or equal preference of fixation is achieved and no further improvement of VA is obtained in two successive follow-up visits.

Liquid crystal display glasses: In this novel therapy, eyeglasses alternate between clear and opaque lens before the fellow eye. Principle of intermittent occlusion is employed and may be associated with better compliance. Few authors report that LCD glasses to be efficacious to patching.[44,45]

Penalization

Here, eye with better vision is defocused by using cycloplegics or altering spectacle glass lens. Indications are

noncompliance to patching, presence of latent nystagmus and as a maintenance therapy. Works best when non amblyopic eye is hypermetropic.

Atropine for penalization proved to be as effective as occlusion. Although the occlusion group had a quicker VA improvement, at the end of 6 months of treatment, there was an equal improvement of VA for the 2 groups, and it was maintained in long-term follow-up (up to 15 years). In addition to those who used daily atropine, patients who used atropine once a week showed improvement in VA and had better compliance.[46] Modest improvement of 4.5 lines (95% confidence interval, 3.2-5-8 lines) was obtained in severe amblyopic patients in 3 to12 years of age group.[47]

There is a high rate of recurrence after the end of amblyopia treatment with similar rates for occlusion and atropine (approximately 25%). This rate was 4 times higher in children who did not have a gradual taper of their treatment for at least 5 weeks following the resolution of amblyopia. Factors also linked with greater recurrence rates included better VA at the end of treatment, greater number of lines of improvement, and previous history of recurrence.[48] Children patching with near work for part of the patching time had no significant improvement than children who patched with no near work as part of the patching regimen[49] (ATS 6).

Surgery to treat cause of amblyopia

The ideal period to treat the causes of deprivation in humans is within the first 6 months of life; after that, the chance to ensure the effectiveness of treatment and achieve normal results decreases rapidly. Unilateral cataracts are more ambyogenic and should be tackled energetically. Dense bilateral cataracts not treated by 3 months of age will almost assuredly lead to the development of nystagmus, which will severely limit VA permanently.[50] In all cases, surgery should be followed by intense amblyopic treatment [Figure 4].

Ideal management option in children with strabismic amblyopia is that alignment surgery should be performed after amblyopia is treated completely. However, Guidelines by the American Academy of Ophthalmology indicate that strabismus surgery may be done prior to completion of amblyopia therapy (AAO PPP Esotropia and Exotropia 2012; RCO Guidelines 2000) and each case is to be individualized and treated accordingly.

Pharmacological therapy

Inadequacy and noncompliance of conventional occlusion therapy led to greater interest in pharmacological therapy.



Figure 4: Occlusion therapy after uniocular cataract surgery

Levodopa-carbidopa

Levodopa-Carbidopa combination is the most extensively studied drug. Levodopa is a precursor of dopamine known to influence visual system at cortical level (levels of retinal dopamine was found to be decreased in deprivation amblyopia).[51] It either extends or reactivates the visual systems sensitive period of neural plasticity. Carbidopa was included which prevents peripheral conversion of dopamine and prevent its gastrointestinal side effects. Augmenting conventional occlusion, effect in older age groups and treatment of residual amblyopia were thought to be its advantages. However, it was seen that daily levodopa + 2-h patching does not produce statistical improvement in VA compared to patching alone (PEDIG2015). And also, there was regression of treatment effect after cessation of therapy. Sofia *et al*. reported statistically significant visual gains sustained at 1 year of follow up in treatment naïve children who had full time patching and levodopa compared to group with patching and placebo (levodopa dose was 3 times higher than in PEDIG study).[52]

Citicoline (cytidine 5'-diphosphocholine)

Citicoline is an important constituent involved in the biosynthesis of cell membrane phospholipids on administration crosses the blood–brain barrier and gets incorporated into the cell membrane phospholipids. It has been shown to increase the levels of norepinephrine and dopamine levels in CNS, offering neuroprotection in hypoxic and ischemic condition. Initially adults in whom citicoline + patching was tried demonstrated improvement in VA but it was not sustained on cessation of the drug. Similarly, studies in children also showed promising results. However, most of these studies of citicoline failed to include follow-up periods beyond 3–6 months and are to be cautiously interpreted.[53,54]

Newer drugs

Citalopram is a selective serotonin reuptake inhibitor (SSRI) which is thought to work on neuro modulatory systems of brain. Clinical trials are going on in the field of adult amblyopia. In normal human subjects, SSRI treatment has been shown to augment visually evoked potentials. In a few adult patients with amblyopia SSRI (citalopram) enhanced VA improvement when combined with 2 weeks of occlusion therapy, but effects in the population were not significantly different from placebo.[55] Another study pairing SSRIs with video game training demonstrated that while video games improved VA, no added value of the SSRI treatment was observed.[56] It is thought that such behavioral and pharmacological manipulations engage similar neuro modulatory pathways, and a ceiling effect is reached and further improvements are not possible.

Another drug mentioned under trial is Donepezil, a cholinesterase inhibitor that is typically used to treat Alzheimer's disease, to boost cholinergic signaling, and recover vision in amblyopic patients.

Researchers are of opinion that pharmacologic therapy is to be combined with other treatment strategies to target plasticity within specific brain regions. Results in research studies in this matter are awaited.

Refractive Surgery

Refractive surgery is indicated in children who are noncompliant to spectacle wear and children with neuro behavioral disorders in whom standard treatment modalities are not possible. Photorefractive keratectomy is the preferred method. A study is underway comparing PRK versus nonsurgical treatment of anisometropic amblyopia in children who have failed conventional treatment (PEDIG2019).

Orthoptic therapy

Vision therapy

This modality of treatment (orthoptics) includes a program of visual activities to improve VA and binocular vision. Includes computer programs, prisms, filters, vergence, anti-suppression, and accommodative activities. Eye hand coordination exercises done in office set up followed by home exercises.[56] These activities were promoted as adjuncts to patching. However, there are insufficient evidence to support efficacy of this treatment.[57]

Binocular (dichoptic) therapy

This treatment is based on the idea amblyopia is a binocular disease though it mostly presents uniocularly, and forms of balanced binocular (dichoptic) treatment are ideal for restoring normal visual function.[58] These are indicated in children with no squint and those with small angle strabismus (with some amount of binocularity) [Figure 5]. High contrast image is projected in front of amblyopic eye and low contrast image in front of normal eye. Children playing the game employ allocation of spatial localization and localization of low contrast fast moving targets. This is thought to improve vision in amblyopic eye. Several games incorporated to iPad are available. For example, "Falling blocks" game (anaglyphic red green glasses used for dichoptic presentation), and Dig Rush game. Early nonrandomized studies were promising.[59,60] Results from a recent randomized trial failed to demonstrate that game play prescribed 1 h/day was as good as patching prescribed 2 h per day.[61] Although research is ongoing, there is insufficient evidence to recommend binocular therapy for treatment of amblyopia.

ADULT AMBLYOPIA

It was found out that visual cortex retains its plasticity into adulthood.[62] Therefore, adult amblyopia may also benefit with treatment. Proper refractive correction is to be instituted followed by patching. Modalities of treatment include perceptual learning, dichoptic treatment, and video games.

Perceptual learning

Principle of perceptual learning is based on the considerable evidence that residual plasticity is present in adult visual brain which can be harnessed to improve functional vision in adult patients with amblyopia. Perceptual training protocols have been developed in which patients practice visual discrimination tasks employing positional acuity, stereo acuity, contrast sensitivity, etc.[63] The performance of repeated activities act by either development of new connections, compensate by unmasking connections that were suppressed or enabling attention to signals that were



Figure 5: Dichoptic therapy

present but weak. Improved pretest to posttest performance and gains in VA were reported when subjects participated in a learnt trial of Gabor signals in a series of 77 adult amblyopes. The neural basis for this is postulated to result from a reduction in lateral inhibition within the brain with training.[64-66] However, perceptual learning has to gain acceptance. Reasons are that outcome measures obtained in amblyopic eye by treatment do not transfer to novel situations (improvement only for task practiced). Studies were conducted with small number of participants. Long-term follow-up of perceptual learning is also lacking. Irrespective of these controversies perceptual learning may become useful in the management of adult amblyopia.

CONCLUSION

Abnormal visual inputs to visual cortex (visual deprivation, strabismus, and anisometropia occurring in critical period of development cause this developmental cortical disorder. Cortical area primarily affected in amblyopia isV1 area but the involvement of higher processing areas is also suggested. The prevalence of amblyopia can be decreased by early screening of children prior 2–3 years. Better outcomes are obtained by early detection and treatment of amblyopia. Conventional treatment methods such as penalization and occlusion are still holding strong. Success rate of amblyopic treatment is about 63% to 83%.[30] No studies are available comparing conventional modalities like occlusion and penalization to newer modalities such as dichoptic treatment and liquid crystal glasses.

It is now thought that there is considerable neural plasticity in amblyopic eye beyond the so-called critical period opening newer avenues for the treatment of adult amblyopia.

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Conflicts of interest
There are no conflicts of interest.

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Major Review

Ocular manifestations of COVID-19 infection: A review of available information

ABSTRACT

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. There is also a surge of information about corneal, uveal, retinal, and neuroophthalmological involvement in COVID-19 infection. This review attempts to determine from various researches published during the time of the pandemic, the various ocular presentations of COVID-19 infection, its significance, correlation to the severity of systemic disease, and its importance as a mode of transmission of the disease. An extensive search strategy was employed to retrieve articles of ocular manifestations of COVID-19 published from January 2020 to date. Conjunctivitis was found to be the most common ocular manifestation, and viral RNA was noted in conjunctiva and tears, posing a risk for ophthalmologists. Other less commonly seen findings in COVID-19 infections include keratoconjunctivitis, blepharitis, retinal changes, and ophthalmoparesis. However, recent studies show increasing reports of retinal and neuroophthalmological manifestations of the COVID-19 infection.

Keywords: Conjunctivitis, COVID-19, novel coronavirus, ocular, ophthalmic, severe acute respiratory syndrome coronavirus 2

INTRODUCTION

One of the most significant medical events in current 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, which presented 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 65,870,030 confirmed cases of COVID-19, including 1,523,583 deaths, reported to the WHO.[3] The clinical features of COVID-19 are ubiquitous, 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 also 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 being accrued on a daily basis, with newer researches contributing to better understanding of the disease process. Over the past couple of months, more and more studies are emerging of the virus affecting not only the conjunctiva, but also other structures such as the cornea, uvea, retina, and the optic nerve. This review attempts to determine from various researches published during the time of the pandemic, the different ocular presentations of COVID-19 infection, its significance, correlation to the severity of systemic disease, and its importance as a mode of transmission of the disease.

METHODS

The aim of this study was to review the available data on the ocular signs and symptoms of COVID-19 infection, demographics, correlation to the severity of systemic

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Table 1: Cross sectional studies of coronavirus disease 19 patients with ocular manifestations

Name of research	Number of subjects	Results	Time course of ocular manifestations	Conclusions
Chen *et al*.[6]	535	Conjunctival congestion was noted in almost 5% patients. It was more seen in patients with a history of hand-eye contact and noted to occur more in patients with severe COVID-19 disease	Most of the patients presented during the course of the illness	Conjunctival congestion could provide a clue to the severity of the COVID infection. Patients may present early in the course of the disease with conjunctival congestion, so taking a conjunctival swab is extremely important
Guan *et al*.[7]	1099	Conjunctival congestion was noted in 0.8% of patients. More than half of the cases were patients who had more severe systemic manifestations		Ocular symptoms probably occur more frequently in patients with serious COVID-19 virus infections
Güemes-Villahoz *et al*.[8]	301	Self-limited conjunctivitis was noted in 11.6% of these patients. It was not correlated to the severity of the disease	Time interval from the start of COVID symptoms to conjunctivitis was 6 days	The authors infer that 1 in 10 COVID patients would develop conjunctivitis. The conjunctivitis was self limited and disappeared without treatment unlike adenoviral conjunctivitis, which could have a more prolonged course
Abrishami *et al*.[9]	142	About 65% of patients had ocular findings and the frequency was proportional to disease severity. The most common ocular finding was conjunctival hyperemia, but the most common in ICU patients was chemosis. Tearing was the most common symptom		There was a high frequency of ocular manifestations in hospitalized COVID patients and probably ocular manifestations could be a sign of more severe COVID disease. It could be a presenting sign of COVID and this should be kept in mind in all patients presenting with ocular manifestations, red eye in particular
Zhou *et al*.[10]	121	8 patients (6.6%) showed ocular symptoms. Only one of these eight patients had a positive result for SARS-CoV2 infection in the conjunctiva. Of the eight patients with ocular manifestations, seven were classified as having severe or critical COVID infection		Ocular symptoms did not correlate strongly with conjunctival swab positivity
Rokohl *et al*.[11]	108 (nonhospitalised PCR confirmed COVID cases)	69.4% of the patient had at least one ocular symptom. Most common ocular symptom reported was burning sensation, followed by epiphora and redness	Ocular manifestations occurred 1.96 ± 3.17 days after the start of COVID-19	Ocular involvement in COVID-19 is relatively high and may be grossly underreported
Bostanci Ceran and Ozates[12]	92	21.5% of patients had at least one ocular finding. The most common ocular sign was hyperemia, and the most common symptom was photophobia. Patients with ocular findings were more likely to have elevated ESR, CRP, and neutrophil counts		Patients with ocular involvement were noted to be older and febrile. The authors conclude that old age, fever, high levels of acute-phase reactants, and high neutrophil/lymphocyte ratio are risk factors for ocular involvement in COVID-positive patients
Savastano *et al*.[13]	80 patients (1 month after recover from COVID-19 infection)	RPCP density was lower in SARS-CoV2 patients compared to controls (using OCT and OCT angiography). 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
Invernizzi *et al*.[14]	54 COVID-19 patients and 133 unexposed subjects	Retinal arterial and venous diameter was more in COVID-19 patients compared to controls. Venous caliber was larger in more serious cases. 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. It was inversely related to the duration between onset of systemic symptoms and the time of taking the photograph. This points to the role of inflammatory mediators and peak venous caliber occurs when the levels of inflammatory agents are highest

contd...

Table 1: Contd...

Name of research	Number of subjects	Results	Time course of ocular manifestations	Conclusions
Pirraglia *et al*.[15]	46 (severe COVID-19 pneumonia patients)	7% of the patients had bilateral conjunctivitis. One patient had probable opportunistic fungal chorioretinitis		No retinal involvement due to the SARS-CoV2 virus was noted in this group of patients
Wu *et al*.[16]	38	Almost 32% of the patients had conjunctivitis	One patient had epiphora as the first symptom of COVID-19 infection	Ocular manifestations were seen most in patients with severe systemic manifestations or abnormalities on blood testing
Meduri *et al*.[17]	29	About 58.6% of the COVID positive patients had ocular findings. Signs of blepharitis and conjunctival hyperemia were the common signs, and burning sensation was the commonest symptom		Tear analysis did not reveal presence of SARS-CoV2. There was a significant correlation between blepharitis like symptoms and the duration of the disease and conjunctival hyperemia and severity of disease in this group of patients
Shemer *et al*.[18]	16 COVID positive patients	Conjunctival injection was seen in 19% of COVID positive patients and was correlated with loss of taste and smell	Conjunctival injection presented before respiratory symptoms in 2 patients and late in 1 patient	Conjunctival injection was noted to be associated with loss of taste and smell, and the trend was associated for a more severe clinical course

COVID - Coronavirus disease, ICU - Intensive care unit, SARS-CoV2 - Severe acute respiratory syndrome coronavirus 2, PCR - Polymerase chain reaction, ESR - Erythrocyte sedimentation rate, CRP - C-reactive protein, RPCP - Retinal peripapillary capillary plexus, OCT - Optical coherence tomography, RNFL - Retinal nerve fiber layer

Table 2: Case series of COVID-19 patients with ocular manifestations

Name of research	Number of subjects	Results	Time course of ocular manifestations	Conclusions
Marinho *et al*.[19]	12	Retinal and OCT changes were noted in 12 patients 11-33 days after developing symptoms of COVID-19	11-33 days after the onset of COVID-19 symptoms	The OCT changes could be associated with the neurological manifestations of COVID-19. Similar lesion have been noted in animal studies
Scalinci and Trovato Battagliola[20]	5	Acute conjunctivitis was seen in 5 cases of COVID-19	These patients did not develop any systemic symptoms	Ocular surfaces have a great tropism for ocular surfaces, and viral RNA is found in tears. This emphasizes the infectivity of tears and also the importance of adequate protection among health-care workers

COVID - Coronavirus disease, OCT - Optical coherence tomography

disease if any, and its importance from a public health point of view.

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 coronavirus or COVID-19 or SARS-CoV2, or eye or ophthalmology or ocular, either singly or variably combined. Databases searched included PubMed, Scopus, and Embase.

The following were the inclusion and exclusion criteria

Inclusion criteria

a. Patients with COVID-19 infection having ocular symptoms
b. Cross-sectional studies, case series, and case reports of the same

Exclusion criteria

a. Studies of other designs
b. Studies not in English language or in which an English translation could not be obtained
c. Studies not demonstrating ocular signs and symptoms of COVID-19 infection.

RESULTS

After fulfilling the inclusion and exclusion criteria, 31 articles were obtained. Of these, 13 were cross-sectional studies [Table 1],[6-18] 2 were case series [Table 2],[19,20] and the remaining were case reports [Table 3].[21-36] Studies conducted purely at the molecular level were excluded.

These studies involved 2804 patients of COVID-19. Of the 13 cross-sectional studies on COVID-19 patients, 11 of them noted that the most common ocular manifestation was a self-limited conjunctivitis.[6-12,15-18] Four of these studies were from China, two from Italy, and one each from Iran, Israel, Spain, Germany, and Turkey. Two of the cross-sectional studies were focused on the retinal signs of COVID-19, which included a reduction in the radial peripapillary capillary

Table 3: Case reports of COVID-19 patients with ocular manifestations

Name of research	Results	Time course of ocular manifestations	Conclusions
Daruich *et al.*[21]	Patient presented with acute conjunctivitis, which was diagnosed by telemedicine consultation	This was followed a few hours later by the occurrence of fever, cough, and dyspnea	Conjunctivitis can be a presenting manifestation of COVID-19 infection. Telemedicine consultations are extremely important in early diagnosis of cases and a high index of suspicion for COVID-19 should be kept in mind in any patient presenting with signs of conjunctivitis during the present conditions
Chen *et al*.[22]	Bilateral acute follicular conjunctivitis	Developed on day 13 of illness	COVID viral RNA was detected in conjunctival swabs from day 13 and disappeared on day 19. This highlights the fact that the eye could be a source of spread of virus and appropriate precautions must be maintained by ophthalmologists
Khavandi *et al*.[23]	Patient presented with burning sensation in the eye and discharge of 2 days duration. Examination revealed the presence of mucoid discharge and follicular conjunctivitis	The ocular manifestation appeared 2 days before onset of fever	Any viral disease during the pandemic should be considered as COVID-19 and the medical staff should take appropriate protective measures
Casalino *et al*.[24]	Patient presented with conjunctivitis of 5 days duration and fever and cough of 3 days duration. Investigations confirmed a diagnosis of COVID-19 infection	Ocular manifestations started 2 days before onset of fever	It is extremely important to ask history of fever and respiratory complaints in any patient coming with viral conjunctivitis. The importance of personal protection of health care workers is vital to protect the frontline staff
Wu *et al*.[25]	The patient who was a 2-year-old child presented on day 7 after testing positive for COVID with conjunctivitis and eyelid dermatitis	Started on day 7, disappeared after 5 days	Children presenting with redness and other ocular abnormalities should be screened for COVID-19 during the pandemic. Furthermore, the conjunctiva and cornea have ACE 2 receptors, thus making it prone to infections by the Coronavirus
Salducci and La Torre[26]	Patient presented with conjunctivitis	The patient was otherwise asymptomatic	The ophthalmologist may be the first physician to examine a COVID-positive patient and should take proper precaution to prevent getting an infection
Marquezan *et al*.[27]	24-year-old healthy man developed bilateral conjunctivitis which resolved in 10 days. He had a history of fever andmyalgia. There was associated loss of smell and taste	Conjunctivitis started 4 days after onset of systemic symptoms	Conjunctival secretions represent a pathway for transmission of the virus
Ozturker[28]	An otherwise asymptomatic patient came to the ophthalmologist with symptoms of conjunctivitis in one eye. Conjunctival swab was negative but nasopharyngeal one was positive		Conjunctivitis can be the only presenting feature of COVID-19 infection. An RT-PCR test should be done in patients presenting with red eye if they have a history of contact with COVID-19 patients
Guo *et al*.[29]	A 54-year-old COVID positive patient presented with conjunctivitis in one eye which was controlled with treatment. Subsequently, he developed keratoconjunctivitis in both eyes 5 days later. This was managed satisfactorily with steroids	Conjunctivitis started 10 days after onset of COVID-19	The authors postulate that viral conjunctivitis is an exogenous event, but the keratoconjunctivitis is probably related to cytokine surge, which occurs as part of the disease process
Cheema *et al*.[30]	Patient presented with keratoconjunctivitis. The conjunctival swab was weakly positive for the SARS-CoV2 RNA		This is the first reported case of keratoconjunctivitis due to COVID-19 infection. Any patient with red eye during the time of the pandemic needs a review of infectious contacts and travel history
Benito-Pascual *et al*.[31]	Patient presented with a 2 weeks 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	10 days later, patient developed dry cough and dyspnoea. PCR of nasopharyngeal swab was positive for COVID	The choroid, neural and vascular endothelium have ACE 2 receptors and represent potential sites of COVID infection
Gascon *et al*.[32]	53-year-old patient presenting with acute vision loss, negative scotoma and dyschromatopsia. Ophthalmoscopy showed retinal hemorrhages and OCT revealed AMN and PAMM-like lesions. Roth spots were also seen	8 days following contact with COVID-19 cases	The retinal lesions could be attributed to the prothrombotic nature of the disease process
Invernizzi *et al*.[33]	54-year-old COVID-19 pneumonia patient presented with 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	10 days after onset of flu like symptoms	Although the ocular condition resolved with steroids, it could represent a thromboembolic complication of the disease process

contd...

Table 3: Contd...

Name of research	Results	Time course of ocular manifestations	Conclusions
Ortiz-Seller *et al*.[34]	A 51-year-old female presented with fever, cough, retro ocular pain and impaired reading. Examination revealed multifocal choioretinitis and bilateral Adie's pupils	Ocular symptoms started 2 days after onset of systemic COVID-19 symptoms	The retinal lesions improved with steroids both ophthalmoscopically and in imaging studies. The Adie's syndrome probably points to the neurotropism of the COVID virus
Belghmaidi et al.[35]	A 24-year-old COVID-19 patient was diagnosed as acute, partial 3rd nerve palsy. She was treated with Chloroquine and Azithromycin and improved completely by the 6th day of treatment	Ocular symptoms started 3 days after systemic symptoms	This report also pints to the neurotropism of SARS-CoV2 virus
Dinkin *et al*.[36]	A 36-year-old man and a 71-year-old female presented with diplopia and ophthalmoparesis. There was associated leg paresthesia and areflexia	This occurred within few days of developing COVID-19 pneumonia	Possibilty of polyneuropathy should be kept in mind

COVID - Coronavirus disease, OCT - Optical coherence tomography, SARS-CoV2 - Severe acute respiratory syndrome corona virus 2, PCR - Polymerase chain reaction, ACE 2 - Angiotensin-converting enzyme 2, RT-PCR - Reverse transcription-polymerase chain reaction, PAMM - Paracentral acute middle maculopathy, AMN - Acute macular neuroretinopathy, CRVO - Central retinal vein occlusion

plexus (RPCP) density and an increase in retinal arterial and venous caliber.[13,14] 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.[19] Another case series of five patients from Italy in the age group of 37–65 years showed that all patients presenting with conjunctival congestion were otherwise asymptomatic.[20] There were eight case reports of conjunctivitis, usually of the follicular type, and which resolved spontaneously without sequelae.[21-28] However, there were two case reports of conjunctivitis due to the SARS-CoV2 virus, which subsequently developed into a keratoconjunctivitis.[29,30] Benito-Pascual *et al*. also described a case of COVID-19 conjunctivitis, which was followed by the development of ocular pain and defective vision, and on examination, revealed panuveitis.[31] There were three reports of patients developing retinopathy following COVID infection.[32-34] Ophthalmoparesis was noted in two case reports with patients presenting with diplopia following COVID-19 infection.[35,36]

DISCUSSION

This review investigated the various ocular manifestations of COVID-19 infection. Conjunctivitis was found to be the most common ophthalmological manifestation. The incidence of conjunctivitis among COVID patients was found to range from 0.8% to almost 65% in different study populations. Wong *et al.* described a prevalence of 0.8%–31.6%.[37] Conjunctivitis was considered a rare COVID manifestation by other authors.[38,39] Amesty *et al*. described it as a rare manifestation of nonsevere coronavirus infection.[40] The type of conjunctivitis noted most commonly seen was the follicular type and was associated in some cases with chemosis, pseudomembranes, and preauricular lymphadenopathy.[6-12,15-18,20] The most common ocular sign noted was conjunctival hyperemia and the most common symptoms were tearing and burning sensation. Chen *et al*., Guan *et al.,* Abrishami *et al*., Bostanci Ceran *et al*., Wu *et al*. and Zhou *et al.* noted that conjunctivitis was seen more often in patients with more severe form of the disease.[6,7,9,10,12,16] Similar findings were also reported by Amesty *et al*.[40] In a study from Israel, conjunctivitis was associated with loss of sense of taste and smell and a more serious clinical course.[18] Conjunctival congestion could thus provide a clue to the severity of the COVID infection. Regarding the timing of onset of conjunctivitis, there were varying reports, some starting before onset of systemic symptoms, some even up to 13 days after disease onset. However, most studies in this review seem to suggest that conjunctivitis tends to occur more in the middle phase of the disease process. There are also descriptions of COVID-positive patients with conjunctivitis, who did not develop any systemic manifestations.[20] Therefore, a high index of suspicion for COVID-19 should be kept in mind in any patient presenting with signs of conjunctivitis during the present conditions. Taking a conjunctival swab would thus seem to be judicious in these circumstances. Paradoxically, many of the studies and case reports state that conjunctival swab was negative despite having a positive nasopharyngeal swab report.[10,17,28] It is also extremely important to ask a history of fever and respiratory complaints and travel history in any patient coming with viral conjunctivitis. The importance of personal protection of doctors should be of prime concern. Telemedicine consults could prove very useful in the diagnosis and reducing the risk to doctors and health-care workers. In most of the cases, conjunctivitis was found to be self-limited and subsided with the reduction of systemic manifestations.[8,20] Conjunctivitis was reported to be seen more often in COVID patients with a history of hand–eye contact.[6] Thus, hand hygiene and frequent handwashing could represent one method to reduce the occurrence of COVID-related conjunctivitis.

Other manifestations of COVID-19 infection include blepharitis in a child with COVID-19,[16] keratoconjunctivitis,[29,30] panuveitis,[31] retinal changes,[13,14,32-34] and ophthalmoparesis.[35,36] Guo *et al.* described a case of bilateral keratoconjunctivitis, which responded to steroids.[29] The authors postulated that keratoconjunctivitis could reflect the cytokine surge which occurs as a part of the disease process. Cheema *et al*. presented a case report of a 29-year-old Canadian woman, who presented with a 1-day history of redness, watering, and photophobia in one eye.[30] Ocular examination showed conjunctival congestion and follicles, a pseudodendrite, and subepithelial infiltrates. Benito-Pascual *et al*. described a case of panuveitis following follicular conjunctivitis and although the uveitis resolved, there was residual disc pallor.[31] S-protein and ACE2 receptors are key pathways for the viral entry into cells.[41] The choroid, neural, and vascular endothelium are rich in ACE2 receptors, which could represent a site for virus adhesion and replication.

With the passage of time in the COVID pandemic, there are increasing reports of retinal involvement in COVID-19 patients. Two cross-sectional studies showed that there were alterations in retinal vasculature, one showing an increase in retinal venous caliber, and this correlates with the peak inflammatory response in the disease process and the severity of the disease process as well.[14] There was also a reduction in RPCP density, and this correlated with the severity of the disease.[13] Both these studies highlight the susceptibility of the retinal vasculature to the virus; it could also represent the virus affinity for the ACE2 receptors in the vascular endothelium. There were two reports of COVID-positive patients presenting with scotomas. Examination in one of them showed the presence of retinal hemorrhages, Roth's spots and a clinical picture resembling acute macular neuroretinopathy and paracentral acute middle maculopathy (PAMM).[32] The other patient showed a picture resembling an impending CRVO.[33] Both cases point to the prothrombotic nature of the disease as reported systemically as well.[42] There was also a case presenting with multifocal choroiditis (with choroidal hypoperfusion on imaging) and an Adie's pupil, which represent the affinity of the virus for the vascular endothelial ACE2 receptors and the neural tissue as well.[34]

There were two cases of ophthalmoparesis. Belghmaidi *et al*. reported a case of a 24-year-old confirmed COVID-19 patient who presented with sudden onset of diplopia and strabismus and was diagnosed as acute, partial third nerve palsy. She was treated with chloroquine and azithromycin and improved in 6 days. The authors suggest that this represents the neurotropism of the virus.[35] Dinkin *et al*. reported two cases of a 36-year-old male and a 71-year-old female, who presented with diplopia and ophthalmoparesis. There was associated leg paresthesia and areflexia. This points to a picture of polyneuropathy, again highlighting the neurotropism of the virus.

CONCLUSIONS

Although conjunctivitis is the most common ocular presentation of COVID-19 viral infection, other parts of the eye including the retina and the optic nerve may be affected. With the passage of time, there are increasing reports of the virus affecting the retina and neuroophthalmological manifestations are being reported with increasing frequency. A conjunctivitis may precede or may not be followed by any systemic manifestations; therefore, it is very important to consider the possibility of COVID-19 in every case of red eye. A detailed travel history and a history of fever and cough are extremely important. Conjunctival swabs may help to confirm the diagnosis in suspicious cases, but they may be negative in a high proportion of cases. Conjunctival congestion is seen more often in severe COVID-19 infection, thus a red eye in a proven COVID-19 patient may be the harbinger of severe systemic symptoms. Hand–eye contact has been noted to be an important factor in the pathogenesis of COVID-19 conjunctivitis, underlining the importance of hand hygiene and frequent handwashing. The viral RNA has been detected in the conjunctiva of patients with COVID-19 having conjunctivitis; thus, ophthalmologists are particularly prone to get infected. Special precautionary measures should be adopted when examining patients presenting with red eye. Vision testing is also important in these patients to rule out posterior segment affection. The ophthalmologist during the time of the pandemic should keep his eyes open to the possibility of the SARS-CoV2 virus affecting every part of the eye. As the vaccine seems within reach and with increasing knowledge about the virus, the sense of panic and fear among populations may abate, but until then, it is best to take care, stay safe, and practice hand hygiene and social distancing to overcome this challenging situation.

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Conflicts of interest
There are no conflicts of interest.

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Adaptive designs for clinical trials

ABSTRACT

The gold standard for interventional studies is the randomized controlled trial (RCT). The RCT follows a linear path with prespecified plans and a little option for flexibility within its implementation. The RCT is also resource and time-intensive and can be a limitation in epidemics or pandemics where more rapid responses can reduce adverse effects. Adaptive designs (ADs) allow for continuous evidence-based modifications to key elements of trial design even as data collection is going on. Reduced use of resources, reduced time to complete the trial, flexibility in the allocation of participants to study arms and improved likelihood for scientifically valid trial results are added advantages with AD. ADs can be applied from early-phase trials to confirmatory trials. In this paper, we introduce key aspects of AD that Ophthalmologists can apply to clinical trials in Ophthalmology. We briefly introduce the rationale for AD, commonly used terminology, and design elements.

Keywords: Adaptive designs, clinical trials, design modification, interim analysis, randomization

CONVENTIONAL FIXED TRIAL DESIGNS

The randomized controlled trial (RCT) is the gold standard design to assess the effectiveness of an intervention in healthcare. Conventional controlled trial designs follow a linear path from the design of the study, implementation of the study, and analysis and interpretation of data after the completion of the trial.[1] The linear path has several advantages with prespecified fixed paths that may improve the validity and reliability of results. However, the fixed linear path has several major disadvantages. These trials need more resources, time, personnel and hence are limited to a smaller number of institutions or triallists.[2,3] Phase III trials usually take a long time to answer clinically relevant questions as the answers are analyzed only on completion of the trial. A previous study has reported significant delays in patient recruitment and enrolment in clinical trials and an increase in the median time from protocol approval to completion of data collection in trials.[4]

Conventional trial designs need specific clinical or public health inputs to determine the sample size. These include factors such as outcome variability, treatment intensity, treatment duration, outcomes, and effect sizes that may not be available to determine sample size.[5,6] The amount of variability in real-life situations compared to the controlled environment of a trial is a factor to consider. Statistical methods that rely on the commonly used frequentist methods will lead to larger sample sizes partly because of the additional variability to be factored in and when trials compare interventions whose effectiveness differs by smaller margins.[2] The larger sample sizes lead to more delays in enrolment and trial completion, and more time and resources to complete the trial and for completion of the analysis. Invariably, this results in more noncompleted trials, a longer lead time for interventions, and increased costs to the public as research and development costs are transferred to the consumer.

Fixed trial designs do perform interim analysis at fixed intervals, with interim stopping rules and exit criteria. However, a disadvantage of the fixed trial design is the

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inability to add a newer, possibly better, intervention to the trial or drop an underperforming intervention from the trial. A comparison of results at a single endpoint as a dichotomous significant or nonsignificant outcome differs from real-world health-care situations, where evidence is a dynamic process of change that accumulates over time. Changes can be done in a fixed trial design method only after completion of the entire trial and through a new trial study. The inability to make optimal use of ancillary information and new information as it arises delay the transition of trial results into clinical and policy domains. The time delays assume greater significance during epidemics and pandemics where rapid responses are needed. It is therefore essential to improve operational efficiency, analytic efficiency, and application of results to a larger population within a reasonable time frame and cost.[2,4,5,7-10]

WHAT ARE ADAPTIVE DESIGNS?

An adaptive design (AD) is described as a clinical trial design that modifies aspects of an ongoing trial based on predetermined strategies and using trial data as it is collected while retaining the validity and integrity of that trial.[11] Adaptive methods are described from the 1960s with gradual progress to wider acceptance by the clinical community and trial lists.[11-16] The United States Congress passed the 21st Century Cures Act in 2016 with instructions to the Food and Drug Administration to provide updated guidance on AD.[17]

ADs offer the possibility to adapt [Table 1], based on a predetermined plan, one or more of the following: A reassessment of the study sample size, allocation to different treatment arms, number of subjects in each arm with a focus to recruiting more subjects likely to benefit, abandon ineffective treatment or doses, and early stopping of the trial either because of success or lack of effectiveness.[18-21] The actual power of the study at any point during the trial is assessed by event-based evaluations and sample size reassessments.[18,21] The randomization ratio can be changed during the trial using response adaptive randomization so that newly enrolled patients are more likely to be assigned to the favorable treatment arm.[19] Trial eligibility criteria and outcome evaluation can be adapted using adaptive enrichment such that modifying eligibility criteria, clinical or biochemical outcomes to enroll patients from a subgroup that has a more favorable response.[20] Seamless adaptive trial designs allow for the continuation of the trial from one phase to another, usually from Phase II to Phase III trials with the results from the Phase II trial determining the initial allocation ratio, planned total sample size, and a potentially enriched population group for the subsequent Phase III.[20,21]

The AD introduces a continuous review-adapt element to the linear path of the fixed trial design [Figure 1] so that the efficiency of the trial is improved.[22] These continuous reviews and adaptations are based on preplanned interim analyses and are not ad hoc or unplanned decisions. Modifications to the trial design based on these interim analyses are implemented without affecting the integrity and validity of the trial. Integrity implies that trial data and processes have not been compromised and that there is no data loss or leakage at the interim analyses stage.[23] Validity implies that the trial will answer the original research question including treatment effects, *P* values and confidence or credible intervals using the appropriate statistical methods.[24-29]

PLANNING AND INTERPRETATION OF ADAPTIVE TRIALS

Fixed trial designs and AD share many similarities, but the AD needs more extensive pretrial planning to determine the interim analyses and possible modifications. Fixed trial designs have interim analyses to determine if the trial should be stopped early, however, these analyses are based on monitoring boundaries that are not adaptive.[30] ADs use decision rules that are prespecified before starting the trial. The most common include rules to terminate treatment arms or the trial and modifications of the allocation ratio between treatments based on the interim analyses.[9] Other

Table 1: Some types of adaptive designs

Adaptive design elements	Process
Hypothesis	The trial hypotheses are adapted based on the results of the interim analysis. These include preplanned shift from single to multiple hypothesis, between null and alternate hypothesis and between primary and secondary endpoints of the trial
Group sequential	Interim analyses lead to prespecified adaptations such as sample size re-estimation, change of treatment arms (modify, delete, add), changing study endpoints, modifying dose and/or treatment duration or adapting randomisation schedules
Randomization	Results are observed continuously, and the randomization scheme is adjusted so that patients enrolled later in the trial have a higher probability of randomization to the more effective treatment arm
Treatment switching	Allows investigator to switch a patient's treatment from the initial assignment to an alternative treatment due to lack of efficacy, disease progression or safety issues associated with the initial treatment
Sample size re-estimation	Flexible sample size adjustment based on interim analysis of data
Seamless transition	Combines the objectives of the Phase II investigational stage with the Phase III efficacy or confirmatory stage into a single study protocol without stopping the patient enrolment process

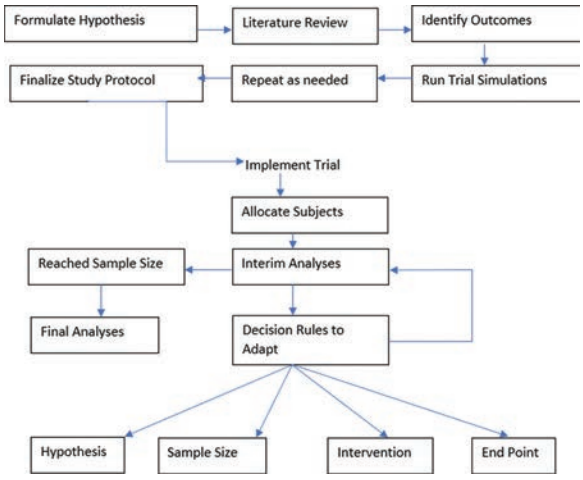


Figure 1: Adaptive design planning process

decision rules include predefined quantitative criteria for re-estimating the sample size or narrowing patient eligibility or picking new arms for more optimal dose-response escalations. The outcomes to consider and the effect of the choice of the outcome on the design, time needed to measure outcome and relevance must be considered. The outcomes of interest must be clinically relevant and correlate with the primary outcomes of the trial.[9] Shorter times to observe the outcome, and therefore collect sufficient interim data, can help to achieve efficiency and ethical gains with adaptations before the trial is terminated.[9] The patient information sheet and consent forms should include details of all possible planned adaptations. It is recommended that the analyses plan and decision rules are determined in consultation with a biostatistician to ensure the validity of the results.

Fixed trial designs usually report differences in interventions as effect sizes, a difference in means or proportions, a *P* value and 95% confidence intervals around the point estimates. These are used to form a dichotomous opinion if there is a significant or nonsignificant difference between the treatment arms. Other metrics that are used to interpret trial results include the accuracy of estimation, the probability of identifying the true best treatment and the best treatment dosage. Data analysis in AD, however, needs combining data from different stages of the trial. Computing estimated treatment effects, *P* values and confidence with similar statistical approaches used in a fixed trial design may lead to errors as the AD can impact the estimated treatment effect.[31] The use of pretrial simulations and appropriate statistical techniques help to reduce errors in determining differences in treatment effects. Several statistical methods are useful to find treatment effects in AD including unbiased estimators, bias-corrected maximum likelihood estimators, median unbiased estimators, shrinkage approaches, and bootstrapping.[32-37] Computation of the *P* values, confidence intervals, and type 1 errors depend on the estimation of treatment effects and need appropriate statistical techniques with adjustment for multiple testing.[38] Several Bayesian methods offer advantages over the commonly used Frequentist methods to determine appropriate effects as multiple tests of the data is statistically possible without adjustment in a Bayesian framework.[39-45] We are not going into a detailed explanation of the statistical processes in this paper.

The methods used for interim analyses can affect the results of the trial. An operational bias can be introduced as the knowledge of or speculation of interim results can alter investigator and patient behavior.[46,47] Careful consideration must be given to the confidentiality of the data analysis process, who had access to the data, and the possible role of trial sponsors in the decision-making process. Operational bias can also be introduced through changes in the care provided and assessment of outcomes and undermine the validity and credibility of the trial unless these are carefully planned changes and analyzed appropriately. These can introduce heterogeneity of the study population (as patient eligibility and enrolment may change) and needs exploration of key patient characteristics and results by different stages of the trial and treatment groups.[8]

CONCLUSION

AD offers several advantages compared to the fixed trial design including the ability to limit exposure of participants to unnecessary treatments, enrolment of participants to more promising treatment arms, the ability to stop the study early, and limiting the possibility of underpowered trials through interim analyses and sample size reassessments. These translate to reduced time to completion of the trial and lower costs that can translate to additional benefits to the end consumers. However, the advantages of AD must balance with the detailed planning and biostatistical support needed for AD compared to the fixed trial design and frequentist method of analyses.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Small incision lenticule extraction versus photorefractive keratectomy: A comparative study

ABSTRACT

Purpose: The purpose of the study is to compare the objective and subjective quality of vision following small incision lenticule extraction (SMILE) and photorefractive keratectomy (PRK). We compared the postoperative safety, efficacy, predictability, refractive stability, contrast sensitivity, and spherical aberration changes in two groups over a 1-year follow-up period. **Materials and Methods:** This was a retrospective comparative study of 1-year duration. Fifty eyes of patients who underwent SMILE and 50 eyes of patients who underwent PRK were selected based on the inclusion and exclusion criteria. **Methodology:** Standard preoperative evaluation for all patients included corneal topography, refraction, anterior segment, retina evaluation, and intraocular pressure. Uncorrected visual acuity, best-corrected visual acuity, spherical aberration, and contrast sensitivity were measured preoperatively followed by 1, 3, 6, 9, and 12 months postoperatively. **Results:** Ninety-six percent of the eyes of patients who underwent SMILE and 92% of the eyes of patients who underwent PRK achieved postoperative refraction within ±0.5 D of the intended target refraction. No eyes in both the groups had any loss of visual acuity. Both procedures induced statistically significant spherical aberrations. However, the difference between the two groups was not statistically significant ($P > 0.05$). One hundred percent of eyes in SMILE and PRK group were noted to have a stable postoperative refraction till the last follow-up. Contrast sensitivity was better in eyes of patients who underwent SMILE comparing to PRK. **Conclusion:** Overall, both SMILE and PRK have shown excellent safety, efficacy, and predictability for correction of myopia and myopic astigmatism. SMILE is better in terms of refractive accuracy and quality of vision.

Keywords: Contrast sensitivity, photorefractive keratectomy, small incision lenticule extraction, spherical aberration, visual outcomes

INTRODUCTION

Small incision lenticule extraction (SMILE) and photorefractive keratectomy (PRK) are two flapless procedures for the correction of myopia. PRK is a surface ablation procedure that induces significant postoperative pain, relatively slow visual recovery, and corneal haze.[1-3] SMILE is a novel form of "flapless" surgery, where the lenticule is extracted through a smaller corneal incision.[4] It is useful for the correction of myopia up to −10 D SEQ and astigmatism up to 5 D. In SMILE, the visual outcome is generally good, and the time to return to normal life after surgery is short.[5]

This study has been undertaken with the aim of comparing the spherical aberrations, predictability, safety, stability, efficacy, and contrast sensitivity changes of SMILE and PRK as both of them are flapless procedures for the correction of myopia and of studying their long-term results.

MATERIALS AND METHODS

This was a retrospective study done in patients who underwent SMILE and PRK. Fifty eyes of patients who underwent SMILE and 50 eyes of patients who underwent

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PRK were selected and were followed up for 1 year. Patients in the 18–40-year age group with myopia and myopic astigmatism, stable refraction for more than 1 year, manifest myopic refraction spherical equivalent (SE) up to 10.0 D, and astigmatism up to 4 D were included in the study. Patients with residual stromal bed <300 μm, suspicion of keratoconus on corneal topography, ocular inflammation, trauma, and infection were excluded from the study. Patients with severe dry eyes and the use of any systemic or ocular medication were also excluded from the study.

This study was accepted by IRB and was in accordance with the ethical standards of the Institutional and/or National Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

All patients received the same preoperative examinations: uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA), cycloplegic refraction, detailed fundus evaluation, contrast sensitivity, intraocular pressure, topography, and dry eye evaluation. Spherical aberration was calculated from the topography data over a 6 mm diameter central corneal zone. All aberrometry measurements were made in the same room with the same dark lighting conditions for all patients. Manifest refraction, UDVA, CDVA, corneal topography data, and spherical aberration were recorded at 1, 3, 6, 9, and 12 months postoperatively. Visual acuities were converted to logMAR before the statistical analysis.

SMILE was performed using the 500 kHz VisuMax femtosecond laser (Carl Zeiss Meditec, Jena, Germany) using a standard surgical technique. The following parameters were used: cap thickness, 120 μm; cap diameter, 7.5 mm; lenticule diameter, 6.5 mm with a transition zone of 0.1 mm; cut energy, 1.4 μJ; and spot and tracking distance, 2.0–3.0 μm. The back of the intrastromal lenticule was created from the periphery to center of cornea. The anterior lamellar cut was subsequently created from center to periphery of cornea, which extended toward the surface to create a 2–3 mm incision, from which the stromal lenticule was extracted. A thin blunt spatula was used to separate the lenticule, which was then grasped with a pair of forceps and removed. The corneal interface was flushed with balanced salt solution.

Alcohol-assisted corneal epithelial removal was performed over a 9.0-mm optical zone centered over the pupil. 20% alcohol in distilled water was dropped into a 9.0-mm well and kept in contact with the epithelium for 50 s and then absorbed with a dry cellulose sponge. The eye was then washed with balanced salt solution. A blunt spatula was then used to remove the loosened epithelium. Stromal ablation was performed with MEL 80 Excimer Laser using a 6.5-mm optical zone. After the stromal ablation, a circular cellulose sponge soaked with mitomycin C 0.02% (0.2 mg/mL) was placed on the cornea for 20 s. The eye was then copiously irrigated with a balanced salt solution to remove the residual mitomycin C. A bandage contact lens was placed over the cornea at the end of the surgery.

The patients on whom PRK was performed were instructed to apply one drop of 0.5% moxifloxacin (4 times/day) and artificial tears until the epithelium was healed. When the epithelial defect was completely closed, the therapeutic contact lens was removed, and 1% prednisolone (4 times/day) was added to the regimen for 10 days. This was followed by less potent steroids (Lotepred) which was then tapered over 2 months. The patients on whom SMILE was performed were instructed to use 0.5% moxifloxacin (4 times/day), 1% prednisolone (4 times/day), and artificial tears starting 3 h after surgery. The dosage of eye drops decreased over time, and the eye drops were continued for 1 month.

Full refractive and visual assessments were performed at the end of 1 week and at 1-, 3-, 6-, 9-, and 12-month intervals. All adverse events were also documented. Uncorrected visual acuity (UCVA), BCVA, spherical aberration, and contrast sensitivity were measured during the follow-up period and at the end of 12 months. Contrast sensitivity was measured with Pelli–Robson contrast sensitivity chart, and the mean spherical aberration on a 6-mm pupil zone was measured using VISANTE AS-OCT.

The various outcome measures were postoperative safety, efficacy, predictability, refractive stability, contrast sensitivity, and spherical aberration changes in the two groups over the follow-up period. Safety was defined as the number and percentage of eyes losing two or more lines of best spectacle-corrected visual acuity. Efficacy was defined as the percentage of eyes with an UCVA of 20/20 or 20/40 or better. Predictability was the proportion of eyes achieving a postoperative SE within ±0.50 D of the target at 6 months of follow-up.

Statistical analysis was performed using IBM SPSS Statistics 19.0 (SPSS Inc., Chicago, IL, USA). Visual and refractive outcomes, efficacy, and safety were evaluated at different time points. Paired *t*-test and independent samples *t*-test were used. $P < 0.05$ was considered statistically significant.

RESULTS

The average age of patients who underwent SMILE was 25.8 years and that of PRK was 22.7 years. Among the PRK group, 40 (80%) patients were female and 10 (20%) patients were male [Figure 1]. In the SMILE group, 32 (64%) patients were female and 18 (36%) patients were male [Figure 2].

The other preoperative and 12-month postoperative parameters are listed in Table 1.

All surgeries were uneventful without any intraoperative complications. No postoperative complications, such as wound dehiscence, inflammation, and infection, were observed in any patient.

Using paired *t*-test, it was found that both procedures induced statistically significant spherical aberrations as compared to the preoperative spherical aberrations ($P < 0.05$).

Using independent samples *t*-test, it was found that even though, postoperatively, spherical aberration was found to be more in the PRK group (0.4918) as compared to the SMILE group (0.4020), the difference between the two groups was not statistically significant ($P = 0.35$). Spherical aberration changes over time in both groups are shown in Figure 3.

Forty-eight (96%) eyes of patients who underwent SMILE and 46 (92%) eyes of patients who underwent PRK achieved postoperative refraction within 0.5 D of the intended target refraction.

No eyes in both the groups were noted to have any complications intra- or postoperatively causing any loss of visual acuity. Ten (20%) eyes of patients who underwent SMILE had an improvement in visual acuity (unaided) as compared to preoperative BCVA by half to one line. Five (10%) eyes of patients who underwent PRK noted this improvement. Comparison of safety in both groups is shown in Figure 4.

All fifty (100%) eyes in the SMILE and PRK group were noted to have postoperative refraction which was stable from 1-month postoperative till the last follow-up.

Forty-eight (96%) eyes of patients who underwent SMILE achieved a postoperative UCVA of 20/20. Forty-five (90%) eyes

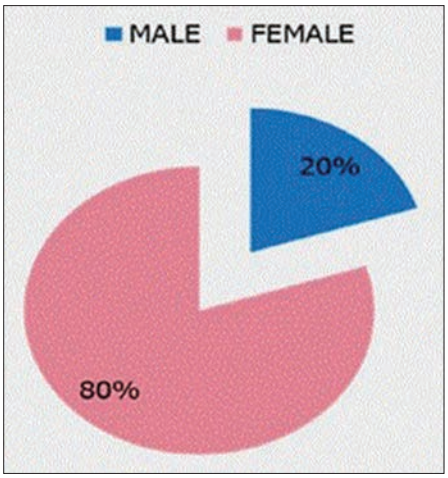


Figure 1: Gender distribution in photorefractive keratectomy group

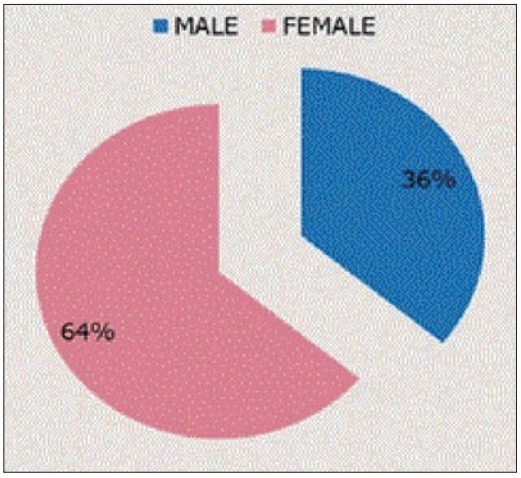


Figure 2: Gender distribution in in small incision lenticule extraction group

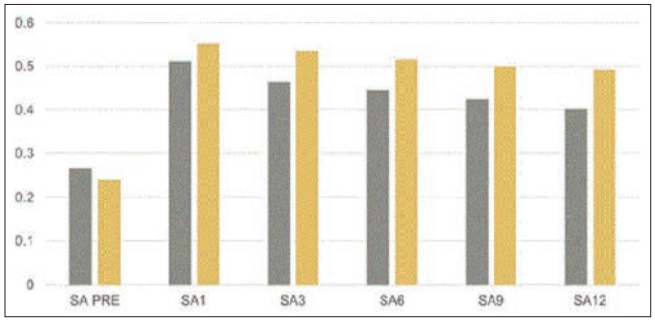


Figure 3: Spherical aberration changes over time in in small incision lenticule extraction and photorefractive keratectomy

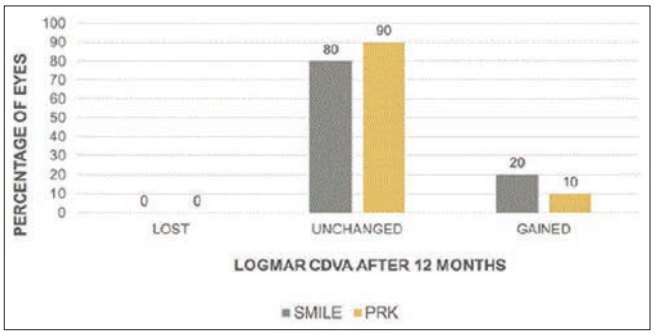


Figure 4: Comparison of safety in in small incision lenticule extraction and photorefractive keratectomy

of patients who underwent PRK achieved a postoperative UCVA of 20/20.

There is no significant difference in postoperative UDVA in SMILE and PRK groups ($P = 0.52$). Comparison of efficacy of small incision lenticule extraction and photorefractive keratectomy is shown in Figure 5.

Contrast sensitivity was better postoperatively in SMILE versus PRK group.

Using independent samples *t*-test, the difference between the two groups was not statistically significant ($P = 0.720$).

Contrast sensitivity changes in SMILE and PRK are shown in Figure 6.

DISCUSSION

The current study showed that SMILE was more effective in low-to-moderate myopic correction compared to PRK at 12 months. Although both procedures were found to be similar in safety, visual rehabilitation was quicker after SMILE compared to PRK.

Ninety-six percent of eyes had postoperative refraction within ±0.5 D in the SMILE group, whereas 92% had within ±0.5 D in the PRK group. This difference in the postoperative refraction can be attributed to the differential healing response between the two procedures. PRK utilizes ultraviolet light from excimer laser to reshape the corneal curvature through direct photoablation. SMILE uses femtosecond laser in near-infrared spectrum to achieve the cutting effect within the cornea through photodisruption. The main advantage of femtosecond laser compared to excimer laser is its high cutting precision with minimal collateral damage and associated cellular and structural changes.[6]

Variation in hydration of the corneal stroma is the most likely cause for underablation or overablation of stromal tissue.[4,7,8] In PRK, after the removal of epithelium, the stroma is exposed to hydration changes before refractive correction. On the other hand, in SMILE, the refractive lenticule is cut by a femtosecond laser before any disturbance of the stroma. It is likely that this difference contributed to greater predictability.

Adjunctive mitomycin C has been demonstrated to prevent post-PRK corneal haze, especially for high myopic correction.[9] Mitomycin C could delay healing and induce apoptosis of anterior stromal cells, modifying the healing response.[10,11]

Similar study on SMILE versus PRK conducted by Ganesh *et al*. showed similar predictability, HOA, and contrast sensitivity changes. Efficacy and safety were found to be higher in SMILE group, while stability was comparable in both groups.[12] Yildrim *et al*. reported that predictability of SMILE group was 92% and PRK group was 89%. Both groups had same efficacy and safety. Stability was found to be more in SMILE group.[13] In this study, HOA was found to be higher in the SMILE group probably because they used aberration-free ablation platform in PRK.

Shah *et al*. demonstrated that 79% of all eyes had a UDVA of 20/25 or better after SMILE.[14] The efficacy that we achieved

Table 1: Comparison of pre-and post-operative parameters in small incision lenticule extraction and photorefractive keratectomy groups

PARAMETERS	SMILE	PRK
PRE OP LOGMAR UCVA	1.12	1.12
SE PRE OP	-4.1+/-2.010	-3.245+/-1.514
SE POST OP 12	-0.15+/-0.20	-0.14+/-0.20
SA PRE OP	0.2676+/-0.0925	0.24012+/-0.0450
SA POST OP 12	0.4019+/-0.1286	0.4918+/-0.0828
CS PRE OP	2.196+/-0.1164	2.202+/-0.1110
CS POST OP 12	2.211+/-0.0822	2.202+/-0.1110



Figure 5: Comparison of efficacy in in small incision lenticule extraction and photorefractive keratectomy

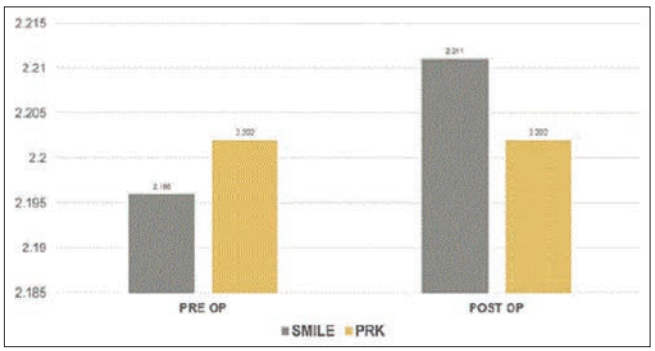


Figure 6: Contrast sensitivity changes in in small incision lenticule extraction and photorefractive keratectomy

Table 2: Comparing similar studies

AUTHORS	PREDICTABILITY	HOA	EFFICACY	SAFETY	CONTRAST SENSITIVITY	STABILITY
Sekundo *et al*			88%-S	88%-S		4% REGRESSION
Ganesh *et al*	97%-S 85%-P	P>S	100%-S 97%-P	100%-S 95%-P	S>P	P=S
Yildrim *et al*	92%-S 89%-P	S>P	S=P	S=P		S>P
Shah *et al*			79%-S			
Diakonis *et al*						6% REGRESSION
Aslanides *et al*	85%					

in our study with SMILE was slightly better than that of previous studies. This finding may be caused by the slightly lower myopic correction in our study.

In our study, no significant haze developed after PRK. The mean attempted refractive correction (−3.24 D) was relatively low and likely below the typical threshold of haze formation reported in other studies.[15]

A study conducted by Diakonis *et al*. on PRK with MMC demonstrated 0.21 D changes in manifest refraction from the 3-month to the 12-month follow-up.[16] Furthermore, these authors found that 6% of eyes regressed more than 0.50 D. Diakonis *et al*. employed a different excimer laser platform, and this may attribute for this difference.

Aslanides *et al*. reported that 85.7% of the eyes that underwent PRK to correct high myopia were within ±0.50 D changes.[17] This discrepancy may be attributed to the difference in the intended refractive correction between the two reports (−8.25 vs. −3.24 D).

Comparison of our study with similar studies on SMILE and PRK is shown in Table 2.

Our study results did not include the impact of SMILE and PRK on corneal biomechanics. We did not evaluate changes in epithelial thickness and other higher-order aberrations. We measured preoperative and postoperative SEs only and did not separately record the astigmatic component. We had very few patients with higher refractive error, and most of them underwent SMILE procedure. In lower refractive errors, the SMILE lenticule will be very thin, and the removal may be difficult. The higher refractive error provides an adequate thickness of lenticule for easy and safe removal. We also acknowledge the relatively small sample size and short follow-up duration, which precludes analysis of the long-term stability of our results.

CONCLUSION

Overall, both SMILE and PRK have shown excellent safety, effectiveness, and predictability for correction of myopia and myopic astigmatism. Keeping in view better quality of vision and faster postoperative recovery time, SMILE is a safe option for higher refractive corrections. Further studies with a larger number of eyes are needed.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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Original Article

Etiological diagnosis of microbial keratitis in a tertiary care hospital in Lucknow

ABSTRACT

Context: Microbial keratitis is a sight-threatening infection which can lead to devastating outcome if not managed timely and rightly. **Aim:** The aim is to study the etiology and assess the risk factors of infectious keratitis in patients presenting to the Ophthalmology Department in King George's Medical University, Lucknow (Uttar Pradesh), India. **Setting and Design:** The study was conducted at the Microbiology and Ophthalmology Department of King George's Medical University, Lucknow. This was a prospective, observational study. **Subjects and Methods:** A total of 120 corneal scrapings were performed in patients presenting with corneal ulcers between August 2016 and July 2017. Gram staining, KOH mount, and culture on blood agar and Sabouraud's dextrose agar were done for all the scrapings for the identification of bacterial and fungal isolates. **Statistical Analysis:** None. **Results:** Microbial etiology was established 34.17% of scrapings. The most common risk factor was trauma (56.7%) of which vegetative trauma was maximum (31/68). Among 41 positive cultures, 34.14% were bacterial while 65.85% were fungal in etiology. The most common bacterial and fungal isolates were coagulase-negative *Staphylococcus* spp. (50%) and *Aspergillus* spp. (25.93%), respectively. **Conclusion:** Trauma was the most common predisposing factor for microbial keratitis in our setting. Fungal infections were more common than bacterial. The "regional" findings play an important role in public health implications to understand the etiology better and to initiate appropriate treatment.

Keywords: Microbial keratitis, sight threatening, trauma

INTRODUCTION

Keratitis is an inflammation of the cornea produced by infectious organisms or noninfectious agents or stimuli.[1] Microbial keratitis is a potentially sight-threatening infectious corneal inflammation, which can be caused by bacteria, virus, fungi, or parasite.[2] In some developing tropical countries, corneal infections are the second most common cause of monocular blindness after unoperated cataract. Corneal ulceration has been labeled as "silent epidemic" in developing countries[3] [Figure 1].

Infectious keratitis imposes diagnostic dilemma because of varied presentations, and prompt antimicrobial treatment should be initiated after clinical and microbiological evaluation to minimize its devastating complications and sequelae.

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It has been found that the etiological and epidemiological pattern of corneal ulcers varies with patient's population, health of cornea, geographical location, and seasonal variation and also with time.[4] Thus, it is important to carry out local studies periodically to be aware of the local disease trend and sensitivity pattern.

This study was thus conducted to study the etiology and assess the risk factors of infectious keratitis in patients

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presenting to the Ophthalmology Department in King George's Medical University, Lucknow (Uttar Pradesh).

SUBJECT AND METHODS

It was a prospective study conducted on 120 patients with corneal ulcers presenting to the cornea clinic in the Department of Ophthalmology in King George's Medical University, Lucknow, from August 2016 to July 2017. Consent was taken from the patients/guardians before enrollment, and patients of all groups were included in the study. Ethical clearance was obtained by Ethics Committee of King George's Medical University.

Data were collected in a brief predesigned format. It included patient's name, age, sex, occupation, duration of symptoms, history of (H/O) ocular trauma, contact lens wear, bathing in pond water, any associated ocular illness, systemic illness, therapy received before presentation, and clinical examination. Corneal scrapings were performed under strict aseptic conditions by an ophthalmologist after instillation of 4% lignocaine without preservative using sterile Bard-Parker needle (No. 15) under slit lamp magnification.[5,6] The material was taken from the leading edge and base of the ulcer. It was placed in a C-shaped streak on the 5% sheep blood agar (SBA) plate and two Sabouraud's dextrose agar (SDA) plates. Any growth on C streak was considered to be significant. Another sample was taken for Gram staining and 10% KOH mount.[7] One set of SBA and SDA plate were incubated at 37°C, and the other SDA plate was incubated at 25°C. SBA plate was considered sterile if no growth was observed within 48 h, and SDA plate was considered sterile if no growth was found in 28 days. The specific identification of bacterial colonies was done by Gram staining, and standard tests using standard laboratory protocols and fungal colonies were identified by their colony characteristics on SDA and morphological appearance of the hyphae and spores in lacto phenol cotton blue mount.

RESULTS

Microbial etiology was found in 34.17% of cases ($n = 41$).

Of 120 clinically suspected corneal ulcers, males showed higher preponderance (68.33%; $n = 82$) when compared to females owing to more outdoor work profile (31.67%; $n = 38$). The most common age group of presentation was 41–65 years (46.67%, $n = 56$), and majority of the patients belonged to the rural background (85%; $n = 102$). Out of the patients involved in outdoor work, farmers were maximum affected (73.9%; 51/69).

H/O ocular trauma could be elicited in 56.67% ($n = 68$) of the patients, and injury due to vegetative material (45.59%; $n = 31$) was the leading cause of ocular trauma.

Around 57.5% ($n = 69$) of the affected individuals presented to the outpatient department after >4 weeks of symptoms as majority of them had sought medical aid from local practitioners or quacks or local medical shops and visited our hospital mainly when their symptoms were either not resolving or worsened [Table 1].

Fungal isolates were recovered from 22.50% ($n = 27$) of samples [Figure 2] whereas bacterial isolates from 11.67% ($n = 14$) of samples. *Aspergillus* spp. (25.93%; $n = 7$) was the most common isolated fungal isolate followed by *Fusarium* spp. (18.52%; $n = 6$) and *Alternaria* spp. (18.52%; $n = 5$). Coagulase-negative *Staphylococcus* spp. (CONS) predominated the bacterial isolates (50%; $n = 7$), while *Pseudomonas* spp. (0.83%; $n = 1$) was the least common bacterial isolate [Tables 2 and 3].

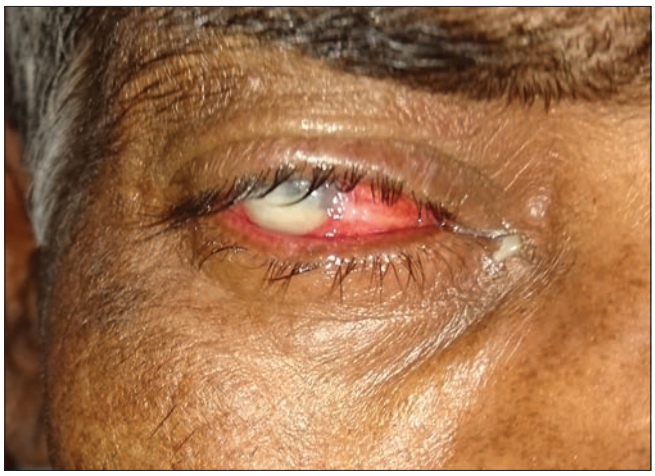


Figure 1: Corneal ulcer



Figure 2: Growth of fungal spp. on Sabouraud's dextrose agar

Taking culture as the gold standard, the sensitivity and specificity of 10% KOH are 81.5% and 78.5%, respectively, and the sensitivity and specificity of Gram stain are 29.6% and 93.5%, respectively, for the fungal isolates. The sensitivity and specificity of Gram staining for bacterial isolates are 100% and 70.8%, respectively [Tables 4-6].

DISCUSSION

Microbial etiology of keratitis in our study was found to be 34.17%. This is lower when compared to the study by Tewari *et al*. which was 59.3%, the study by Bharathi *et al*. which was 69.59%, or other Indian studies.[4,8] All the patients had unilateral eye involvement.

Female: male ratio was found to be 1:2.16. This is more attributed to outdoor work done by males. Affected patients generally belonged to 40–65 years of age group (46.67%) which is similar to Chhangte *et al*. where 53.9% of cases were of the same age group.[5]

Table 1: Distribution of patients according to history of prior consultation/treatment before presenting to the hospital (*n*=120)

Prior consultation	Number of patients	Percentage
No prior consultation	11	9.17
Prior consultation	109	90.83

Table 2: Bacterial pathogens isolated from 14 culture-positive bacterial keratitis cases

	Number of patients	Percentage (*n*=14)	Percentage (*n*=120)
Sterile	106		88.33
Bacterial positive	14		11.67
Coagulase-negative *Staphylococcus* spp.	7	50.00	5.83
Staphylococcus aureus	4	28.57	3.33
Staphylococcus pneumoniae	2	14.29	1.67
Pseudomonas spp.	1	7.14	0.83

Table 3: Fungal pathogens isolated from 27 culture-positive fungal keratitis cases

	Number of patients	Percentage (*n*=27)	Percentage (*n*=120)
Sterile	93		77.50
Fungal positive	27		22.50
Acremonium spp.	1	3.70	0.83
Alternaria spp.	5	18.52	4.17
Aspergillus fumigatus	3	11.11	2.50
Aspergillus flavus	4	14.81	3.33
Aureobasidium pullulans	1	3.70	0.83
Candida albicans	2	7.41	1.67
Cladosporium spp.	1	3.70	0.83
Curvularia spp.	4	14.81	3.33
Fusarium spp.	6	22.22	5.00

Majority of the patients were from rural background (around 85%). Major bulk of Indian population live in rural areas, and they are more involved in manual labor; thus, they have more chances of injuries and infections as compared to desk job people in the urban setup. Trauma as a whole accounted for 56.67% of all the cases, thus being the most common predisposing risk factor. Similar findings of trauma have been seen in Paraguay with 48%,[9] Eastern Nepal with 53%,[10] South India with 65%,[11] and Eastern India with 83%[12] of all the keratitis cases.

Most of the traumatized patients were outdoor workers (70.59%).[13] Sitoula *et al.* also showed trauma to be the most common risk factor in their study.[14] Among the patients enrolled, 47.50% had encountered corneal trauma mainly from vegetative matter and less commonly from dust, insect bite, or any other cause. Out of these, 15% (n = 18) of the patients had systemic illness in the form of blood pressure, diabetes, rheumatoid arthritis, facial palsy, seizure, thyroid, asthma, or heart surgery, while 15% (n = 18) patients presented with ocular injuries such as cataract, glaucoma, vitreous prolapse, or any operative procedure. None of our patients had H/O using contact lenses.

Of 120 corneal scrapings performed, 65.83% (n = 79) of the cultures were sterile and 34.17% showed growth. Total microbial etiology of 34.17% is less as compared to other

Table 4: Comparison of Sabouraud's dextrose agar culture and 10% KOH mount for fungal isolates

	SDA culture		Total
	Positive	Negative	
10% KOH positive	22	20	42
10% KOH negative	5	73	78
Total	27	93	

SDA – Sabouraud's dextrose agar

Table 5: Comparison of blood culture and gram stain for bacterial isolates

	Blood culture		Total
	Positive	Negative	
Gram stain positive	14	31	45
Gram stain negative	0	75	75
Total	14	106	

Table 6: Comparison of Sabouraud's dextrose agar culture and Gram stain for fungal isolate

	SDA culture		Total
	Positive	Negative	
Gram stain positive	8	6	14
Gram stain negative	19	87	106
Total	27	93	

SDA – Sabouraud's dextrose agar

studies by Tewari *et al*. and Bharathi *et al*. with a recovery of 59.3% and 69.59%, respectively, but is in accordance with study by Gupta *et al*. where 38.3% of cases were culture positive.[4,6,15]

Bacterial growth was seen in 11.67% ($n = 14$) of the cultures, whereas 22.50% ($n = 27$) of the cultures showed fungal growth. Growth rate is lower when compared to other studies such as Bharathi *et al*. (34.98%), Tewari *et al*. (38%), Kumar *et al*. (26.5%), and Basak *et al.* (28.8%).[4,6,12,16] This reduction in bacterial corneal ulcers at the referral centers can be credited to better treatment outcome at peripheral centers since the introduction of topical fluoroquinolones in the late 1990s.[17]

Among 11.67% of the bacterial cultures positive, 50% ($n = 7$) showed growth of CONS, 28.57% ($n = 4$) of *Staphylococcus aureus*, 1.67% ($n = 2$) of *Streptococcus pneumoniae*, and 7.14% ($n = 1$) of *Pseudomonas* spp. The isolation rate of CONS (60%) is almost similar to the study by Tewari *et al*.[4] The most common bacterial infection in Nepal and South India was *S. pneumoniae* and in Ghana and Bangladesh was *Pseudomonas* spp. Gram-positive bacilli were not observed in the present study. This differs from various studies that have demonstrated a 4.0%–12.5% incidence.[12,18,19] We isolated only one Gram-negative isolate which was *Pseudomonas* spp. This is in contrast to other studies where the isolation of Gram-negative organisms has been as high as 39.7% by Tewari *et al*.[4]

Fungal positivity was seen in 22.50% of the cultures. This isolation rate is lower when compared to studies done by Sitoula *et al*.(70%), Leck *et al*. (44.1%), Srinivasan *et al*. (51.9%) and Basak *et al*. (59.3%) but is almost similar to Bharathi *et al*. (32.26%).[5] Out of the 22.50% positive fungal cultures, *Aspergillus* spp. is the most common fungal isolate (25.93%; $n = 7$) followed by *Fusarium* spp. (22.22%; $n = 6$), *Alternaria* spp. (18.52%; $n = 5$), *Curvularia* spp. (14.81%; $n = 4$), and *Candida albicans* (7.41%; $n = 2$), and 3.7% ($n = 1$) cases showed *Acremonium* spp., *Aureobasidium pullulans*, and *Cladosporium* spp. *Aspergillus* spp. has been found to be a common fungal isolate in West Bengal (Basak *et al*.), Nepal (Upadhyay *et al*), and Bangladesh (William *et al*.) as well.[3] In contrast, the prevalence of fungal corneal ulcers in developed countries was as low as 20% in Florida[20] to 3% in the UK.[21] However, *Fusarium* spp. was the most common cause of fungal keratitis in South India, Western India, and few studies from abroad.[8,12,22,23] *A. pullulans* was an unusual pathogen isolated in the study.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Bridging the gap – Where do we stand? An inquiry into awareness of diabetic retinopathy among diabetics

ABSTRACT

Introduction: Awareness of diabetic patients with regard to diabetic retinopathy, its treatment options was assessed; as well as relation between gender, disease duration, socioeconomic and educational status with awareness of diabetic eye involvement. **Methods:** This was a hospital-based cross-sectional descriptive study using a semi-structured questionnaire among diabetic patients attending ophthalmology services of a tertiary care teaching hospital in North Kerala. **Results:** Of 203 patients, 58% were male and 42% were female. Majority belonged to the age group of 61–70 years (35.5%) and duration of diabetes of 1–5 years (28%). Sixty-six percent of patients were aware that diabetes could affect the eye. Awareness of ocular complications was associated with education level of the patients and duration of diabetes. Physicians contributed to awareness in 32% of cases and ophthalmologists in 23%. Most (51%) had an eye checkup only when they had symptoms. Majority (72%) were not aware of treatment options for diabetic retinopathy. Eighty-three percent of patients who knew of ocular involvement underwent screening against 31% of patients who did not. Fifty-one percent of patients who were aware of disease complications were on regular follow-up, as against 33% of patients who were not aware. Lack of knowledge was the most common cause (80%) as a barrier to early ocular screening. **Conclusions:** Awareness of diabetic ocular complications and knowledge regarding eye involvement, treatment, and follow-up are poor. The gap between merely knowing about eye involvement to fully understanding its implications on visual function still remains to be bridged. Hence, campaigns to increase the knowledge of diabetes and its complications should be carried out through electronic, print, and social media. Increased understanding of their disease results in better health-care attitude among patients.

Keywords: Awareness, diabetic retinopathy, education, knowledge, socioeconomic

INTRODUCTION

Diabetes mellitus is a long-standing disease associated with much morbidity and is estimated to affect over 65 million adults in India, with prevalence being higher in South Indian states such as Tamil Nadu and Kerala.[1] Eye involvement in diabetes can range from a troublesome dry eye to sight-threatening retinal involvement, which can be attributed to various factors, the most important of which is the duration of the disease. The WHO reported that India accounted for 22% of global visual impairment cases. The National Blindness and Visual Impairment Survey India 2015–2019 reports that diabetic retinopathy contributes to 1.2% of blindness and 3.6% of cases of visual impairment. "The global diabetes prevalence in 2019 is estimated to be 9.3% (463 million people), rising to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045."[2] As the number of diabetics in the population increases, a proportionate rise in people suffering from visual impairment due to diabetic retinopathy is expected. Poorly controlled comorbid conditions such as hypertension, dyslipidemia, and renal disease also increase the risk and severity of diabetic retinopathy. Various studies have documented that good control of blood glucose levels and of other comorbid conditions, as mentioned earlier,

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can delay the onset and progression of diabetes-related eye complications.[3]

Diabetic retinopathy can be easily detected by a dilated fundus examination by ophthalmologists and trained physicians. Early detection and prompt treatment is key to the prevention of vision loss caused by diabetic retinopathy. Diabetic screening programs are being organized by various eye care organizations incorporating telemedicine facilities and smartphone-based strategies. The success of such screening programs also depends on the individual patients' knowledge about their disease and its complications, as well as willingness to present for evaluation and to undergo treatment and follow-up as advised by the eye care provider.

This study aims to determine the awareness level of diabetic patients with regard to their disease and its ocular complications and to assess preferred practice patterns among the study group.

METHODS

This was a hospital-based cross-sectional study involving diabetic patients attending the ophthalmology clinic at a tertiary care center in North Kerala. Consecutive patients with diabetes over a period of 6 months were included in the study after obtaining informed consent. Exclusion criteria included age <18 years, patients with diabetes of <3-month duration, diabetes secondary to pancreatic disease, steroid-induced diabetes, juvenile diabetes, gestational diabetes, and subnormal mentation, and those who were unwilling to participate. The study was conducted after approval from the institutional research and ethics committees in accordance with the Declaration of Helsinki.

Data were collected using a semi-structured questionnaire administered in the local language using the interview method. Statistical analysis was carried out using the SPSS Inc. PASW Statistics for Windows, Version 18.0. Chicago: USA. Frequency and percentages were used for all categorical variables. Chi-square test was done to check the association for categorical variables. The association was considered significant with $P \leq 0.05$.

Awareness of diabetic patients with regard to diabetic retinopathy was assessed in relation to collected variables such as gender, age, socioeconomic status, level of education, and duration of the disease. The source of knowledge regarding diabetic complications was determined as well as practice patterns with respect to diabetic disease control, ocular screening, and compliance to treatment.

RESULTS

Demographic variables

Two hundred and three patients were enrolled in the study, of which 58% were male and 42% were female. Majority of the patients belonged to the age groups of 61–70 years (35.5%) and 51–60 years (34%). More than half, i.e., 57%, of patients belonged to the lower socioeconomic strata, below poverty line, and 43% belonged to above poverty line group.

One hundred and nineteen patients had only primary education (59%), whereas 32% had secondary level of education. Four percent were graduates and 5% had no formal education.

Awareness of ocular involvement

One hundred and thirty-four patients (66%) in this study were aware that diabetes could affect the eye. There was a significant association between awareness of ocular complications and education level of the patients ($P = 0.022$) [Figure 1], as well as with duration of diabetes ($P = 0.027$) [Figure 2]. There was no relation with gender, socioeconomic status, or treatment of diabetes.

Source of knowledge

Physicians contributed to making patients aware in 32% of cases, whereas ophthalmologists were source of information in 23% of people in this study group. An equal number, i.e., 23%, were made aware of diabetic involvement of eyes by their peer group (friends and relatives). Mass media including television and Internet-based media contributed to patient

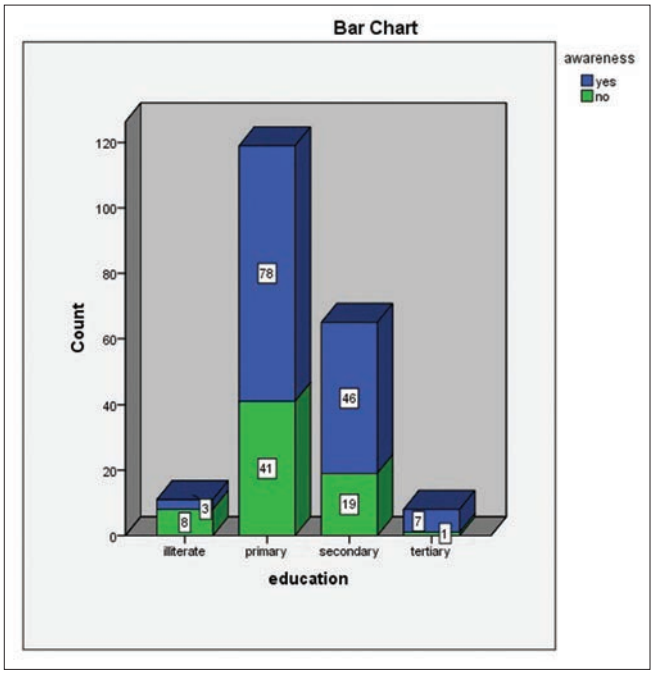


Figure 1: Awareness among different education levels

awareness in 10% of cases, whereas paramedical personnel as a source of information were cited by a mere 2% of patients. Ten percent of these patients gathered information from multiple sources like their physicians, mass media, and peers [Figure 3].

Diabetic eye involvement

Although a significant proportion of the study group were aware of diabetic involvement of the eyes, majority (63%, $n = 85$) of those who were aware only knew that it causes defective vision. Sixteen percent of patients knew that it causes retinal damage, and another 16% were totally ignorant of how diabetes could affect the eye. Only 2% of patients were well informed that diabetes can affect the eye in multiple ways. Few persons were of the notion that diabetes causes cataract, whereas one patient each opined that it can cause an increase in intraocular pressure and foreign body sensation in the eye [Table 1].

Ocular screening

A total of 153 patients had ocular examination for diabetic retinopathy, whereas 50 patients had never had a detailed eye examination. It is interesting to note that 83% of patients who were aware of ocular involvement in diabetes had undergone screening, whereas only 31% of patients who did not know about eye involvement had ocular screening. This difference is statistically significant, $P = 0.001$ [Table 2].

Reason for ocular evaluation

Only eight patients came for ocular checkup on their own. More than half of the study population who did have a detailed ocular examination presented with ocular symptoms such as defective vision and eye pain. The second largest subgroup of screened patients was those who were referred by their treating doctors (physicians >ophthalmologists) [Figure 4].

Awareness of treatment options

It is interesting to note that majority of the patients in the study group, i.e., 72% (146 patients), were not aware of treatment options for diabetic retinopathy [Table 3].

Of the 57 patients who knew that retinopathy could be treated, most (46%) thought that control of their diabetic status would suffice, whereas 25% of patients knew that laser photocoagulation and control of diabetes would help treat their ocular problem. Twelve percent did not know what treatment options were available, 8% thought that laser photocoagulation alone was sufficient, whereas

Table 1: Patients opinion as to how eye is involved in diabetes

Patients opinion regarding eye involvement	Frequency (%)
Diabetes causes defective vision	85 (63.4)
Diabetes causes retinal damage	21 (15.6)
Diabetes can involve the eye, but do not know how	21 (15.6)
Diabetes can involve eye in many ways including retinal damage, cataract leading to defective vision	3 (2.23)
Diabetes causes cataract	2 (1.49)
Diabetes causes increase in intraocular pressure	1 (0.74)
Diabetes causes foreign body sensation	1 (0.74)

Table 2: Screening among patients aware versus those not aware

Awareness	Screening		Total	Pearson χ^2
	Done	Not done		
Yes	111	23	134	0.001
No	42	27	69	
Total	153	50	203	

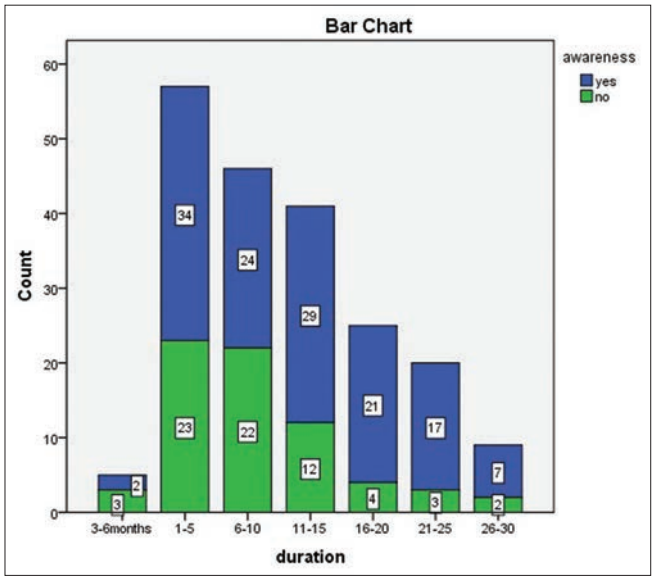


Figure 2: Awareness among patients with varying duration of diabetes

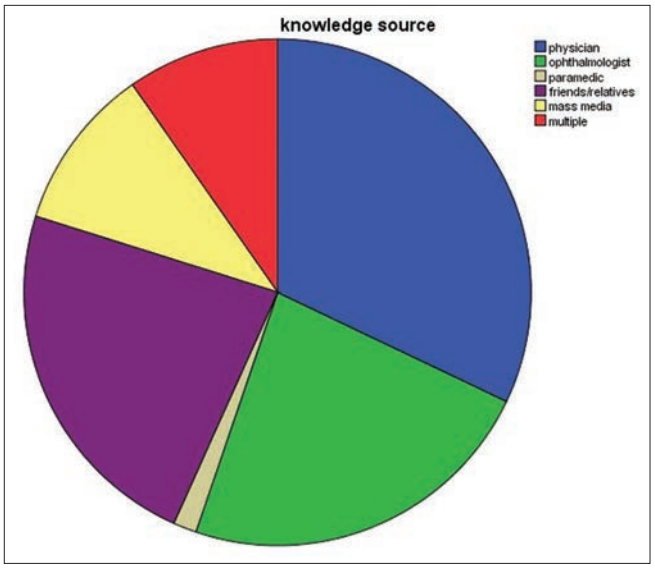


Figure 3: Source of knowledge about ocular involvement

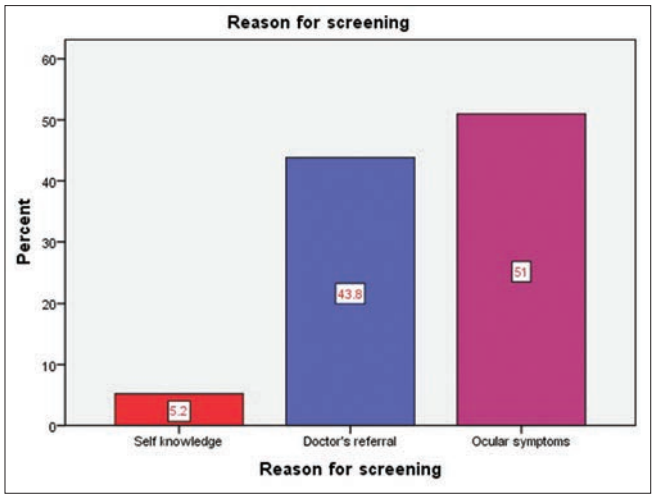


Figure 4: Reasons for ocular screening

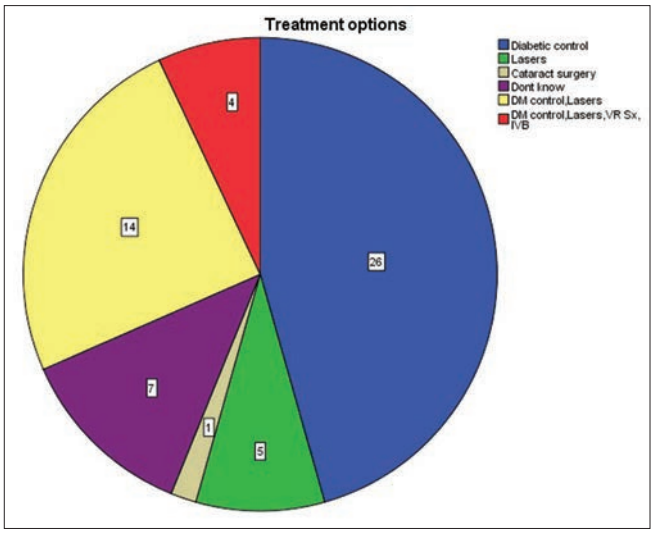


Figure 5: Treatment options known

7% knew that there were multiple options such as laser treatment, intravitreal pharmacotherapy, and surgical options for diabetic retinopathy in addition to good control of their disease. Two percent thought that cataract surgery would help treat diabetic retinopathy [Figure 5]. None of the patients were aware of the significance of controlling comorbid conditions such as hypertension, dyslipidemia, and renal disease.

Awareness versus treatment compliance

Among the persons screened, 51% of patients who were aware of their disease complications were on regular follow-up as advised by the ophthalmologist, as against only 33% of patients who were not aware that diabetes could affect the eye [Figure 6], and the difference in attitude was statistically significant, $P = 0.001$ [Table 4].

Barrier to early ocular screening

Lack of knowledge regarding importance of early ocular screening was the most common cause (80%) cited by the patients for not having an early eye checkup. No specific reason was given by 13%, cost consideration about treatment was cited by 2.5%, time constraint by 2%, and 0.5% did not attend screening, fearing that they would have severe disease.

DISCUSSION

Kerala is a state which boasts of a high literacy rate (93.9%)[4] and a robust health-care system. Unfortunately, it is also facing an epidemic of sorts with regard to diabetes mellitus as reported by Vijayakumar *et al*.[5] Diabetic retinopathy is an inevitable complication of the disease, directly related to duration of diabetes, and is potentially blinding unless detected and treated in early stages of retinal involvement. This study attempts to assess awareness levels of diabetics with regard to ocular involvement and various factors associated with it.

Table 3: Awareness of eye involvement versus treatment options known

Awareness	Treatment options Awareness		Total	Pearson
	Yes	No		χ^2
Yes	49	85	134	0.000
No	8	61	69	
Total	57	146	203	

Table 4: Compliance to medical advice versus awareness

Awareness	Regular ocular follow-up			Total	Pearson
	Not screened	Yes	No		χ^2
Yes	22	69	43	134	0.001
No	28	23	18	69	
Total	50	92	61	203	

This study found that more than half of the study group (66%, $n = 134$) were aware that diabetes could affect the eye. A similar study conducted in central Kerala by Saikumar *et al*.[6] found that 84% of diabetics knew that diabetes could affect the eye. Various studies from other parts of India have shown awareness of diabetic patients to be 77.5% (Dinesh Venugopal *et al*.),[7] 65.3% (Lingam *et al*.),[8] 48.6% (Koshy *et al*.),[9] and 71.9% (Nithin Keshav Srinivasan *et al*.).[10] Studies from developing nations such as Malaysia, Sri Lanka, and Nepal reveal awareness levels of 86% (Tajunisah *et al*.),[11] 81% (Seniviratne *et al*.),[12] 63.3% (Thapa *et al*.),[13] respectively, whereas developed nations such as Sweden showed awareness rates as high as 90.6% (Konstantinidis *et al*.).[14]

In our study, we noticed a statistically significant association between educational status of the participants and awareness levels. Most of the study participants had only primary education (58.6%, 119 patients), 32% ($n = 65$) had secondary level of education, and only 4% ($n = 8$) had graduated. This maybe one reason for relatively lower percentage of

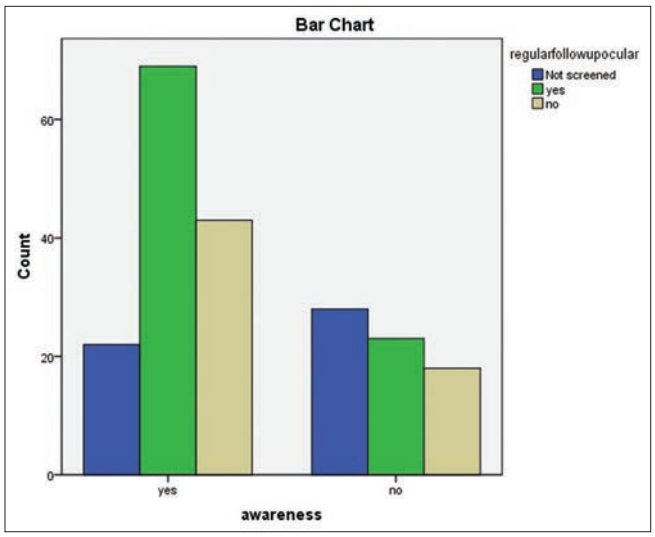


Figure 6: Compliance to treatment among subgroups

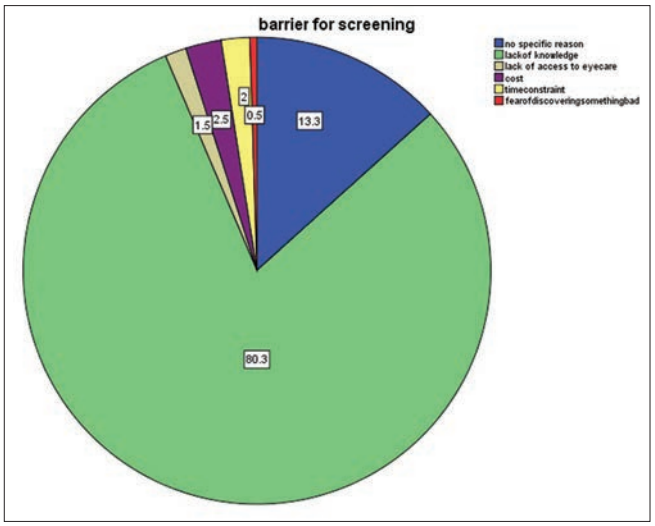


Figure 7: Perceived barrier to treatment in diabetics

awareness level obtained in this study. However, among the subgroups [Figure 1], 66% (78/119) of those who had primary education were aware, whereas this rose to 75% (46/65) and 88% (7/8) among those who completed secondary and tertiary levels of education. Studies by Tajunisah *et al*.,[11] Thapa *et al*.,[13] Dinesh Venugopal *et al*.,[7] and Katibeh *et al*.[15] also showed a positive association between education of the patient and level of awareness.

Duration of diabetes also was significantly associated with increased awareness levels in our study [Figure 2]. Maximum awareness was seen in patients who had the disease for 21–25 years. This may be due to increased number of visits to the physician. This was similarly demonstrated in the study conducted by Koshy *et al*.[9] and Seneviratne *et al*.[12] Another interesting point noted was that there is a higher degree of awareness in patients who are diabetic for 1–5 years, compared to those who have the disease for 6–10 years though the difference is not statistically significant. This may be a pointer toward the success of recent awareness campaigns.

Most of the patients in this study quoted physicians as their (32%, $n = 43$) source of information regarding eye involvement in diabetes. Various other studies have also reported the same.[10,11,15] Ophthalmologists were the second most common source (23%, $n = 31$). 45.2% of physicians who participated in a study by Anchala *et al*.[16] stated that they referred patients for ocular examination at the first visit itself. Ten percent reported that they did retinal examinations by themselves.[16] It is imperative that doctors treating diabetes are made aware of ocular complications as well as the need for periodic eye checkup.[17] Another point noted in our study is the miniscule contribution to awareness (1%, $n = 2$) by paramedical personnel. Namperumalswamy *et al*.[18] also noted that 55% of paramedics who participated were not aware of risk factors for retinopathy and close to three-fourth of them did not know of treatment options such as lasers or vitreoretinal surgery. They also found that there was a dearth of educational material among majority of the paramedics which could be used to promote awareness on diabetes and its complications.[18] This is an area of concern which requires much strengthening and planning. With an ever-increasing diabetic population, it will be necessary to deploy them for screening retinopathy. This has been addressed with due importance in the recently published operational guidelines for diabetic retinopathy screening.[19]

Although majority knew that diabetes could affect the eye in this study, only around 16% knew that it causes retinal damage and only 2% knew that diabetes could affect the eye in multiple ways other than retinopathy. This discrepancy between "awareness and knowledge" has been well documented in previous studies.[6,10,11] This deficiency in knowledge can be addressed by increasing awareness activities through mass media campaigns, diabetic retinopathy screening camps, and exhibitions on World Diabetes Day and World Sight Day.

It was observed that majority of patients were not aware of treatment options for diabetic retinopathy, with most of the patients among both groups (those who knew of diabetic eye involvement and those who did not) being so. Only 9% and 32.6% of participants were aware of treatment modalities in studies by Rajani Kadri *et al*.[20] and Koshy *et al*.[9]

Awareness does lead to increased health-seeking behavior as our study documents that more than three-fourth of participants who were aware (83%, $n = 111$) underwent screening compared to those not aware (31%, $n = 42$).

A statistically significant relation between awareness of retinopathy and good practice pattern regarding retinopathy was also noted by Mahesh *et al*.[21] and Nithin Keshav Srinivasan *et al*.[10] Similarly, among those screened, more than half (51%, $n = 69$) of those who were aware were on regular follow-up against only 33% ($n = 23$) of those who were not aware. Counseling at diabetic care centers and eye clinics regarding treatment, follow-up, and lifestyle changes could help increase compliance among diabetic patients.

Half of the patients (50.9%, $n = 78$) presented for screening when they had symptoms such as defective vision or ocular discomfort. This is comparable to earlier studies which report 27%–45% of participants who present with vision loss.[11,13,22,23] This is not an ideal situation as diabetic retinopathy is easily detectable and treatable in early stages. Screening of diabetic retinopathy can be successfully integrated into the public health system in India,[24] which can reduce the burden of avoidable blindness due to diabetes.

Eighty percent of participants opined that lack of knowledge was the main obstacle for not undergoing ocular examination early [Figure 7]. Lack of understanding of diabetic eye involvement was cited as a barrier to early eye screening in a study by Tajunisah *et al*.[11]

CONCLUSIONS

Diabetics do not fully understand the devastating effects their disease can have on their visual function which can significantly hamper their quality of life. It is important therefore, to conduct campaigns through electronic, print and social media to increase knowledge regarding diabetes and its ocular complications among the public in general,and the diabetics in particular. Enhanced utilization of ground-level health workers and paramedical personnel at clinical establishments should be envisaged. It is encouraging to note that awareness leads to a significant rise in healthy practice patterns in patients. Proposal to integrate screening into the public health system in India is a welcome move from policy-makers and will go a long way to bridge the gap that still exists between "awareness and knowledge" of diabetic retinopathy among diabetics.

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There are no conflicts of interest.

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Original Article

Prevalence of corneal astigmatism in patients undergoing cataract surgery in a tertiary care hospital of Malwa region of Northern India

ABSTRACT

Context: Preoperative corneal astigmatism plays a pivotal role in deciding the outcome of cataract surgery. If the values of biometry prevalent in a particular region are known, it will help the cataract surgeons locally even in the remote areas to optimize the postoperative visual outcome. **Aims:** The aim was to study the prevalence and distribution of different types of corneal astigmatism among the patients in Malwa region of Punjab and its variations according to age. **Settings and Design:** This was a hospital-based retrospective study conducted on 370 patients of Malwa who underwent cataract surgery between December 1, 2017, and July 31, 2018, in a medical college situated in North India. **Subjects and Methods:** The records of the patients were reviewed, and biometric data – K1 and K2 – measured by IOLMaster™ 700 (Carl Zeiss Meditec AG, Jena, Germany) were collected. The data were categorized based on demographic variables, type of astigmatism, and extent of astigmatism. **Statistical Analysis:** The data were subjected to descriptive statistical analysis to yield frequencies, percentages, and means. **Results:** A total of 370 eyes of 370 patients were studied. The mean age of the studied population was 60.43 ± 9.9 years. Nearly 50.54% were males and the rest were females. The mean of K, K1, and K2 was 44.23 ± 1.65 D, 43.75 ± 1.68 D, and 44.71 ± 1.74 D, respectively. Almost 82.16% of the studied population had mean corneal astigmatism <1.5 D. The corneal astigmatism was against the rule (ATR) in 52.16%, with the rule (WTR) in 27.29%, and oblique in 17.83%. With increasing age, there is a gradual shift of astigmatism from WTR to ATR, in both males and females, which peaks in the sixth decade of life. **Conclusions:** Majority of patients in Malwa region of Punjab have corneal astigmatism less than 1.5 D. Against-the-rule astigmatism is more common than other types of astigmatism.

Keywords: Cataract surgery, corneal astigmatism, IOLMaster 700

INTRODUCTION

The technique of cataract surgery has seen drastic changes during the past few decades. Phacoemulsification is now the preferred modality of cataract surgery. Intraocular lens designs have also evolved tremendously during this time. These advancements have led to a significant decrease in the postoperative spherical refractory error. However, the cylindrical refractory error continues to hinder the achievement of full visual potential.[1-5]

Postoperative astigmatism can be either surgery induced or residual of preoperative corneal astigmatism. Surgically induced astigmatism has greatly been reduced by the use of small phacotips and smaller incisions. However, the presence of preoperative corneal astigmatism continues to challenge the final visual outcome. This astigmatism can be addressed by placing an incision on steep axis, use of toric intraocular lens, or limbal relaxing incision.[6]

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Corneal astigmatism depends on the anatomy of cornea, which has regional influences apart from changes based on age and sex. Knowledge of the prevalence and distribution of corneal astigmatism can be helpful to the operating surgeon in deciding among the fore-mentioned techniques for optimizing the postoperative visual outcome. Preoperative corneal astigmatism of population of different ethnicities has been studied in the past.[5,7-13] However, no such study has been conducted for the Malwa region of Punjabi population. We intend to study the preoperative corneal astigmatism in patients who have undergone cataract surgery in our institute. This would help in designing efficient and cost-effective cataract surgery techniques for achieving a better postoperative visual outcome in an area where agriculture is the main occupation and accessibility to gadgets such as IOLMaster™ 700 is not easy.

SUBJECTS AND METHODS

A retrospective study was conducted in a tertiary care medical college of Malwa region, Punjab. Research and ethical clearance was obtained from the institutional research and ethical committee. The demographic and biometric data of patients who had undergone cataract surgery from December 1, 2017, to July 31, 2018, were collected. Exclusion criteria were patient's age <21 years and a history of previous ocular surgery, ocular trauma, and ocular diseases such as pterygium, keratoconus, corneal ectasia, and inflammation. Patients in whom biometric data could not be measured by IOLMaster 700 due to dense cataract were also excluded from the study to avoid any bias due to the usage of different examination tools. IOLMaster 700 was used in our study for biometric measurements because of its ultra-high precision (5 mm or less) and good resolution (12 mm).[14] Patients not belonging to Malwa region were also excluded from the study as we intend to prepare a local database to be used by local cataract surgeons.

Precataract surgery examination included visual acuity assessment, tonometry, refraction, slit-lamp examination, and fundus examination. IOLMaster biometric data were collected prior to dilatation of pupils. The parameters measured were axial length of eyeball and keratometry values (*K*1 and *K*2). Herein, *K*1 represents flat corneal curvature, whereas *K*2 represents steep corneal curvature. *K* value was calculated as the mean of *K*1 and *K*2.

Corneal astigmatism was categorized as with the rule (WTR) when the meridian of maximum curvature was within 30° of vertical 90°, against the rule (ATR) when the meridian of maximum curvature was within 30° of horizontal 180°, and oblique (OBL) if it was neither WTR nor ATR. The patients were divided into groups on the basis of age – 21–30 years, 31–40 years, 41–50 years, 51–60 years, 61–70 years, 71–80 years, and ≥80 years. The data were compiled in Microsoft Excel Spreadsheets. They were categorized by demographic variables and were subjected to descriptive statistical analysis to yield frequencies, percentages, and means.

RESULTS

A total of 370 eyes of 370 patients with cataract were studied. The mean age of the studied population was 60.43 ± 9.9 years (range 21–90). Maximum number of patients were in the age group of 61–70 years (42.16%) followed by the age group of 51–60 years (28.9%). A least number of patients were in the extremes of age groups. There were 187 (50.54%) males and 183 (49.46%) females.

Corneal astigmatism among the studied population ranged from 0 D to 8.48 D, with a mean of 0.96 ± 0.93 D. Majority of the patients had corneal astigmatism of <1.5 D (82.16%) and only 3.51% of the patients had corneal astigmatism of ≥3 D [Figure 1]. The mean *K* value obtained was 44.23 ± 1.65 D, with mean *K*1 value being 43.75 ± 1.68 D (range 37.79–49.18) and mean *K*2 value being 44.71 ± 1.74 D (range 39.85–52.32). The age-wise distribution of mean values of *K*1, *K*2 and *K* are detailed in Table 1.

Of the population studied, 27.29% (n = 101) had WTR astigmatism, 52.16% (n = 193) had ATR astigmatism, 17.83% (n = 66) had oblique astigmatism, and 2.7% (n = 10) had no astigmatism. As the age advances, there was a shift from WTR to ATR astigmatism, in both males and females, with a peak in the sixth decade of life [Figures 2-4].

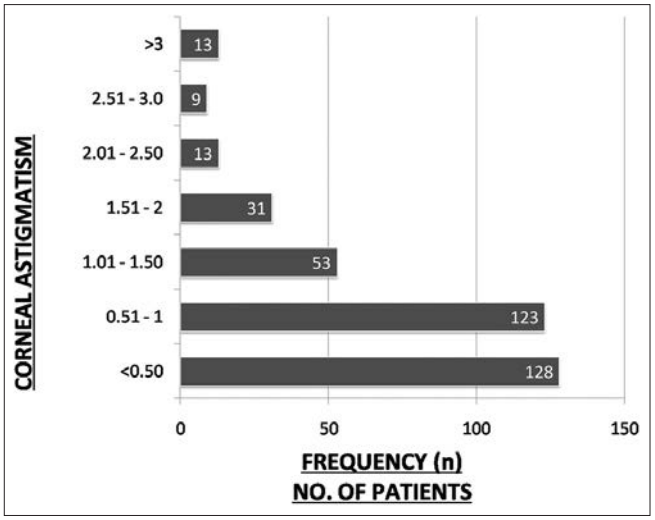


Figure 1: Distribution of amount of astigmatism among the studied population

DISCUSSION

The main components contributing to ocular astigmatism are cornea and lens. Lenticular astigmatism is taken care of and eliminated in patients undergoing uncomplicated cataract surgery, but the persistence of preexisting corneal astigmatism leads to patient dissatisfaction because of some amount of residual unaided blurring or distortion of vision. Studies showing the prevalence and type of corneal astigmatism in patients undergoing cataract surgery are well documented in several countries, but such data are lacking for population belonging to the Malwa region of Punjab.

Ours is the study conducted in a tertiary care medical college of this area which analyzes the prevalence and type of corneal astigmatism in the region. This study will help in enhancing the postcataract surgery satisfaction rate as it will help the surgeons to adopt suitable corrective procedures for elimination of corneal astigmatism, even if costly equipment such as IOLMaster 700 are not handy.

Our study included 370 eyes of 370 patients with a mean age of 60.43 ± 9.9 years, which is similar to the studies done by Rashid *et al*,[15] Chaudhary and Dahal,[16] and Prasher and Sandhu.,[17] which had mean ages of 61.9 ± 8.1, 64.45 ± 12.89, and 59.54 ± 10.96 years, respectively, but much lower from studies conducted by Chen *et al*.,[8] Khan and Muhtsaheb,[5] Ante Ercegovic *et al*.,[10] and Yuan *et al*.[18] This variation for mean age among studies could be attributed to the difference in sample size and racial and ethnic differences in the age of developing cataract. Males and females included in our study were 51% and 49%, respectively, which correspond to the study conducted by Prasher and Sandhu[17] with 49% of males and 51% of females and Yuan *et al*.[18] with 46% of males and 54% of females. This represents equal cataract surgery-seeking behavior in both the genders in the Malwa belt.

The mean corneal astigmatism in our study came out to be 0.96 ± 0.93 D, which is marginally lower as compared to studies done by Prasher and Sandhu[17] Chen *et al*.,[8] and Khan and Muhtsaheb,[5] which reported the mean corneal astigmatism values of 1.04 ± 1.04, 1.01 ± 0.69, and 1.03 ± 0.73 D, respectively. It was much lower than the study conducted by Rashid *et al*,[15] Yuan *et al*.,[18] and Isyaku *et al*.[19]

The range of corneal astigmatism in our study was 0–8.48 D, which is slightly lower than the study conducted by Prasher and Sandhu,[17] with range being 0–9.75 D, but significantly higher than studies conducted in other countries.[5,8,15,16,18,19]

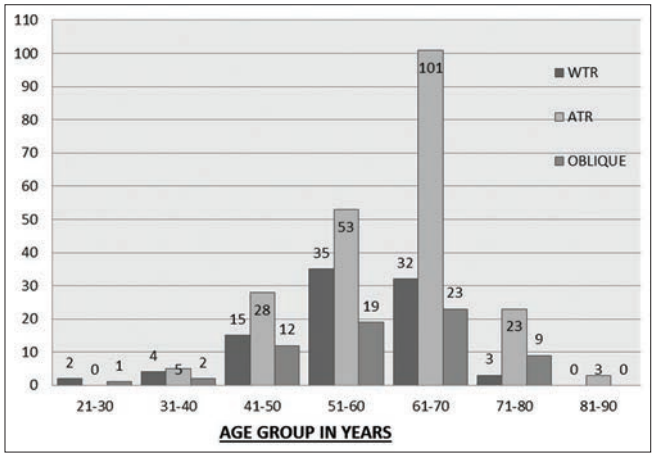


Figure 2: Distribution of different types of astigmatism according to age group

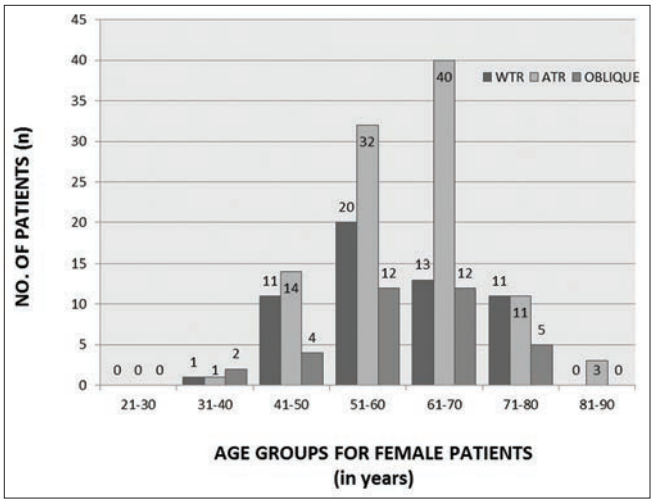


Figure 3: Distribution of different types of astigmatism according to age group in females

Table 1: Mean values of *K*1, *K*2, and mean astigmatism among different age groups

Age (years)	Eyes (%)	Mean *K*1 (Diopters)	Mean *K*2 (Diopters)	Mean astigmatism (Diopters)
21-30	3 (1)	42.3±1.54	42.87±1.31	0.57±0.23
31-40	11 (3)	43.74±1.8	44.34±2.05	0.60±0.39
41-50	55 (15)	44.02±1.95	44.84±1.96	0.78±0.70
51-60	107 (29)	43.75±1.77	44.60±1.82	0.84±0.98
61-70	156 (42)	43.66±1.57	44.76±1.64	1.10±1.01
71-80	35 (9)	43.86±1.44	44.98±1.57	1.11±0.80
81-90	3 (1)	43.60±0.93	44.73±0.61	1.13±0.52

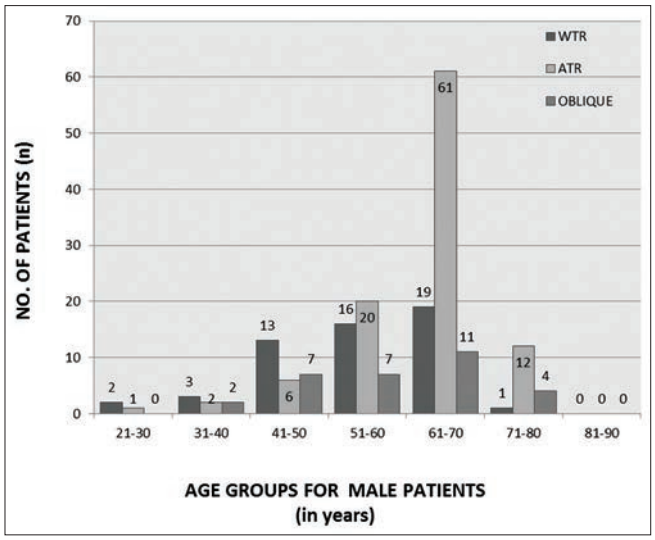


Figure 4: Distribution of different types of astigmatism according to age group in males

Majority of population (82.16%) in our study had corneal astigmatism <1.5 D, which outnumbers the results reported by Prasher and Sandhu[17] of corneal astigmatism <1 D in 59.3% of population. Another study reported astigmatism ≥1 D in 66.9% of the eyes.[19] These values of astigmatism of our study, however, correlate well with a study conducted by Rashid *et al*.[15] in Nepal. The study by Miyake *et al*.[20] observed a prevalence of <1 D of corneal astigmatism to be 63.6%.

More than half of the population under our study had ATR astigmatism (52.16%), with WTR astigmatism being the second largest category comprising of 27.2% population and only 17.83% of population had oblique astigmatism. The percentage of ATR astigmatism in our study was higher as compared to the study by Chaudhary and Dahal[16] (43.6%) and lower as compared to the study by Isyaku *et al*.[19] (56.66%). There are studies by De Bernardo *et al*.[13] and Hoffman and Hutz,[12] which have reported higher prevalence of WTR as compared to ATR.

The variation of results between studies on the Indian population and foreign population and even between different regions of India can be attributed to various factors including difference of sample sizes, geographical and ethical distribution of populations, variation of ocular anatomy according to race, different environmental and lifestyle practices of different races, and the socioeconomic status of the included population. Variations in inclusion and exclusion criteria for populations under different studies and difference in instruments used for taking measurements are also important factors affecting the studies, thus leading to differences in results among different studies.

There are some limitations to our study which include (1) our retrospective study was based on clinical data which may lead to some selection bias, (2) the ocular biometric data were drawn retrospectively from the patients who underwent cataract surgery, and (3) the relationship between biometric parameters and genetics, diet, education, occupation, and severity of cataract could not be established due to lack of relevant data.

CONCLUSIONS

Our study shall provide useful data on the corneal biometry of the region, which can help the local cataract surgeons to individualize cataract surgery in a way that it gives better visual outcomes, which are affordable especially in the population of Malwa, where the main occupation of people is farming.

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Conflicts of interest
There are no conflicts of interest.

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Original Article

Corneal endothelial cell characteristics and central corneal thickness in patients with type 2 diabetes mellitus

ABSTRACT

Purpose: To evaluate the morphological features of corneal endothelium and central corneal thickness (CCT) in patients with type 2 diabetes mellitus (DM) and to correlate them with the duration of diabetes and patients glycemic status. **Design:** This was a prospective, cross-sectional, comparative, hospital-based study. **Materials and Methods:** The present study was conducted on 192 diabetics and 192 age- and sex-matched healthy controls. Corneal endothelial cell characteristics, CCT were measured using a specular microscope. Statistical comparisons were done between the case and controls using the appropriate parametric or nonparametric test. The associations between the various parameters were studied using the Pearson coefficient of correlation. **Results:** The mean corneal endothelial cell density (CECD) in the diabetic group (2521.3 ± 300.7 cells/mm^2) was significantly lower compared to the nondiabetic group (2629.3 ± 221 cells/mm^2) ($P < 0.001$). The mean CCT in diabetic group was significantly higher (532.00 ± 24.88 ∝m) compared to control group (499.47 ± 24.76 ∝m) ($P < 0.001$). The co-efficient of variation though higher and hexagonality though lower in diabetics was not statistically significant. CCT showed a significant positive correlation with duration of DM ($r = 0.566$, $P<0.001$). A weak positive correlation was observed between CCT and HBA1C ($r = 0.271$, $P<0.001$) No correlation between CECD and CCT for diabetics with a duration of >10 years when compared with those with a duration of <10 years was observed. **Conclusion:** Diabetic patients in our study had thicker corneas, decreased CECD, and hexagonality, more irregular cell size than that of age matched controls. However, duration of the disease and the glycemic control did not affect these parameters.

Keywords: Central corneal thickness, corneal endothelium, diabetes mellitus, duration

INTRODUCTION

Corneal endothelial cell changes in diabetic patients have been explained by the assessment of polyol (sorbitol–aldose reductase) pathway in the diabetic cornea.[1] Earlier studies have documented that high glucose levels led to increased activity of the aldose reductase, causing sorbitol build up in the corneal epithelial and endothelial cells. This sorbitol acts as an osmotic agent and leads to the swelling of endothelial cells. Furthermore, diabetes mellitus (DM) diminishes Na+–K+ ATPase activity of the corneal endothelium.[1] This results in the morphological and permeability changes in a diabetic cornea.[2] Endothelial pump function was proven to be affected by decreased ATP production as a result of slowing down of the Krebs cycle in a diabetic cornea.[3]

Corneal endothelial cell studies on diabetic patients have shown variable results. Many studies have shown that even minor changes in the morphology of the endothelial cells may manifest in the disturbances in the tightness of the endothelial barrier.[4,5] An arrest of the human endothelial cells in G1 phase results in the loss of endothelial cells being compensated by expanding of the neighbouring cells.[6] This,

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over a period of time results in corneal edema due to the lack of tightness.[6] The questions that need to be pondered are if these changes are transient during the time of increased blood sugars in the body or permanent, affected by the duration of the disease and if glycemic control has any effect on these changes. There are very few studies correlating the endothelial parameters with the duration and glycemic control, again with conflicting reports.[3,5,7]

We planned to compare the morphological features of corneal endothelial cell in type 2 DM with age-matched, nondiabetic controls using Specular Microscope Tomey EM-4000 (Tomey Corporation, Japan) and correlate these corneal changes with the duration of DM and glycemic control (glycated hemoglobin [HbA1c] level).

MATERIALS AND METHODS

This prospective, hospital-based, comparative study protocol was approved by the University's Institutional Ethical Committee. Our study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all patients before their enrollment in this study. The diagnosis of DM was based on the criteria of the American Diabetes Association (ADA).[7] Patients diagnosed as diabetics, at least 1 year prior to the study and started on anti-diabetic drugs were included as cases. Recruitment of the subjects was based on the medical history and treatment taken by the patients attending the outpatient clinic.

Nondiabetic patients used as controls underwent two casual blood glucose tests in accordance with the recommendations of the ADA[8] to disclose undetected diabetes. Data collected included the duration of diabetes and HbA1c levels.

The exclusion criteria included patients not willing to give written informed consent, postoperative patients, contact lens users, patients with corneal diseases or dystrophies, any ocular traumas such as blunt and penetrating injuries, history of any other systemic illness, patients with glaucoma and retinal diseases not associated with diabetes, any other ocular disease such as dry eye, anterior uveitis, primary angle closure glaucoma, evidence of any corneal pathology on slit-lamp biomicroscopy, and high refractive errors.

The right eye of all the patients was examined using a noncontact specular microscope, Tomey EM-4000 (Tomey Corporation, Japan) with an autoshot option by fixed frame method. The patient was positioned on a chair in front of the specular microscope and made to fix inside the device till the instrument automatically took a clean image of corneal endothelium and measured the parameters. Parameters that were recorded included corneal endothelial cell density (CECD), average cell area (AVG), coefficient of variation (CV) of cell area, percentage of hexagonal cells (6A), and central corneal thickness (CCT). An average of 3 reading was taken for the analysis. Cell density was recorded as the number of cells per square millimeter. The CV of hexagonal cell in the analyzed area was used as an index of variation in cell shape (polymegathism). The percentage of hexagonal cells indicated pleomorphism. CCT varies over the day with cornea being thickest in the morning and gradually becoming thinner.[9] Specular microscopy and CCT were hence measured at the same time of the day 10 p.m. to 12 pm, to reduce the errors related to diurnal variation.

The primary outcome variable studied was the relationship of corneal endothelial cell characteristics in diabetic patients and healthy controls.

The secondary outcome measures included the effect of duration of diabetes and glycemic control on the diabetic cornea.

All data distribution analysis was checked using the Kolmogrov–Smirinov test. Data were evaluated using the descriptive statistics which were presented using mean and standard deviation (SD). Statistical comparisons were done between the case and controls using an appropriate parametric or nonparametric test. The Mann–Whitney test or *t*-test was used as and when required for finding the association between various parameters in diabetic patients and healthy controls. The associations between the various parameters were studied using the Pearson Coefficient of Correlation®. Multivariable regression analysis was used for identifying the influencing factors for cell density with respect to different predictors. These predictors were checked for the modal fit by adding or removing the predictors at each level. The predictors included age, sex, CCT, and percentage of hexagonal cell in the final modal. All the data values of beta coefficients and its standard errors were analyzed. Multi-collinearity was checked analyzing variance inflation factors (VIF). If a high VIF was observed, then the predictor would not be considered in the model. For the regression model, the $P = 0.25$ was (adjusted $P = 0.05$, adj-*P*, *P*/number of predictors in the model) considered for statistical significance. Statistical analysis was performed using Minitab® 17.1.0, © 2013 Minitab Inc.

RESULTS

In this study, corneal endothelial cell parameters of 192 diabetic patients were compared with 192 healthy controls. The mean (±SD) age of the study group was 58.86 (±7.90)

years, and of the controls were 57.95 (±8.79). The mean duration of DM was 7.86 (±5.69) years. Mean HBAIC was 10.12 (±2.69). Table 1 includes the corneal endothelial cell characteristics of right eyes of cases and controls as recorded by a specular microscope. Figure 1 shows (a) specular microscopic image of normal and (b) specular microscopic image of diabetic cornea. The mean endothelial cell density in the diabetic group (2521.3 ± 300.7 cells/mm2) was significantly lower compared to the nondiabetic group 2629.3 ± 221 cells/mm2 ($P < 0.001$). Figure 2 shows the comparison of corneal ECD between diabetics and nondiabetics. The mean CCT in diabetic group was significantly higher (532.00 ± 24.88 µm) compared to the control group (499.47 ± 24.76 µm) ($P < 0.001$). Mean corneal ECD and mean CCT in patients with DM duration >10 years when compared with those with DM duration ≤10 years were found to be insignificant.

Correlation analysis of various predictors such as cell density, average cell area, hexagonality and CCT in diabetics with age, duration, and HBA1C was done. Cell density ($r = -0.167$, $P = 0.021$) showed a significant negative correlation with age. CCT showed a significant positive correlation with duration of DM ($r = 0.566$, $P < 0.001$). A weak positive correlation was observed between CCT and HBA1C ($r = 0.271$, $P < 0.001$).The comprehensive list of correlation coefficients is presented in Table 2.

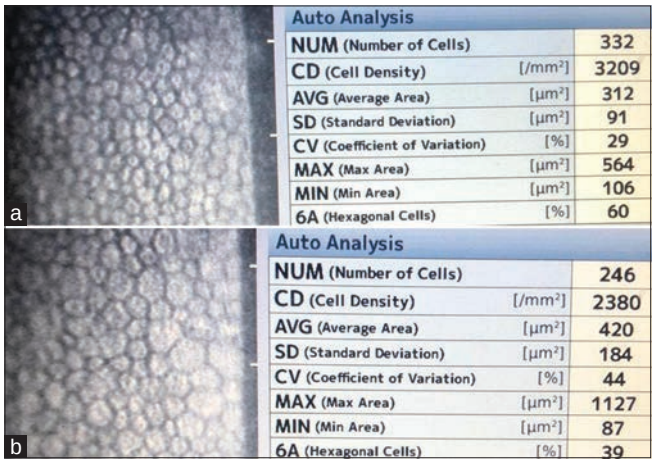


Figure 1: Specular microscopic image of (a) Normal cornea. (b) Diabetic cornea

Regression analysis of corneal ECD with age, percentage of regular hexagonal cells (6A), CV, CCT, and duration of DM found predictor factor average cell area and CV to influence the CECD, as depicted in Table 3. The model was adequate with R2 and R2-adjusted nearly 50%. There was no multicollinearity in the model observed with VIF 1–2.

DISCUSSION

Corneal changes have been observed in patients with hyperglycemia of long duration as a result of compromise in the functioning of the layers of the cornea.[3] All corneal layers are involved in DM in different ways such as corneal endothelial damage, recurrent corneal erosions, superficial keratitis, ulcers, diminished corneal sensitivity, and delayed wound healing.[10] Folds in Descemet's membrane were detected earlier in diabetic patients compared to nondiabetic elderly people.[11] However, the brunt is taken by corneal endothelial cells. Our study demonstrated a significant reduction in corneal ECD in patients with type 2 DM. This finding was comparable to many other studies.[12-14] However, Schultz *et al*.[15] found no difference in ECD in type 2 DM, but demonstrated a significantly higher rate of cell loss in type 1 DM. Módis *et al*.[16] studied corneal endothelium in type 1 and type 2 diabetic patients. They found a statistical reduction in ECD in type 1 in comparison with healthy controls.

Storr-Paulsen *et al*.[17] showed CCT to significantly increase in diabetes. Our study also demonstrated a significant

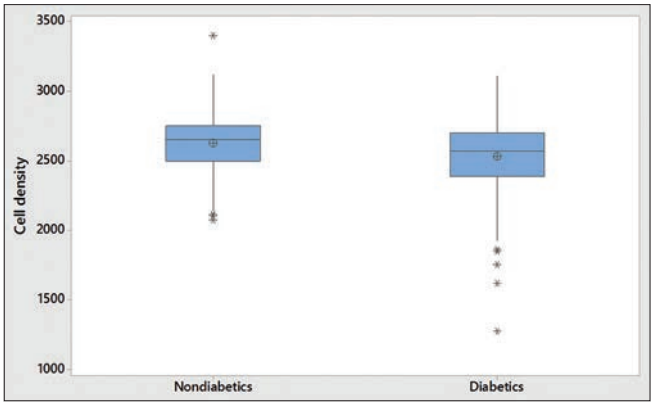


Figure 2: Comparison of corneal endothelial cell density between diabetics and nondiabetics

Table 1: Corneal endothelial cell characteristics of right eyes of case and controls as recorded by specular microscope

Variable	Diabetics	Nondiabetics	95% CI	*P*
Cell density	2521.3±300.7	2629.3±221	−126-−36	<0.001
Coefficient of variation	38.95±16.18	36.854±5.973	−0-2	0.199
Average cell area	401.37±135.02	393±133.52	−35.32-18.58	0.542
Percentage of regular hexagonal cells	45.870±7.261	46.932±5.989	−2.398-0.273	0.19
Central corneal thickness	532.10±24.88	499.47±24.76	26-35	<0.001

The values are presented as mean±SD with 95% CIs of mean differences. $P<0.05$ is considered as statistically significant. CIs – Confidence intervals, SD – Standard deviation

Table 2: Correlation coefficients between corneal endothelial cell parameters and the predictors in diabetics

Pearsons correlation	CD	AVG	CV	6A	CCT
Age	−0.167*	0.134	0.049	0.048	0.098
Duration	−0.103	0.045	−0.024	0.019	0.566*
HbA1c	−0.044	−0.01	0.022	−0.09	0.271*

$P<0.05$ is considered as statistically significant. *$P<0.05$. AVG – Average cell area, CV – Coefficient of variation, 6A – Percentage of hexagonal cells, CCT – Central corneal thickness, HbA1c – Glycated hemoglobin, CD – Cell density

Table 3: Regression analysis of corneal endothelial cell density with predictor variables

Parameters	Coefficient	SE coefficient	*T*	*P*	VIF
Constant	3407	443	7.69	0.000	
Age	−2.45	2.05	−1.19	0.234	1.08
Duration	−2.5	3.42	−0.73	0.466	1.55
AVG	−1.441	0.118	−12.19	0.000	1.05
CV	−2.12	1.09	−1.95	0.052	1.27
6A	2.84	2.44	1.17	0.245	1.28
CCT	−0.361	0.77	−0.47	0.64	1.51

Coefficient, S=215.618, R^2=50.21%, Adjusted-R^2=48.60% for the final model described. Adjusted *P*-value of 0.05 was considered for statistical significance. SE – Standard error, VIF – Variance inflation factor, AVG – Average cell area, CV – Coefficient of variation, 6A – Percentage of hexagonal cells, CCT – Central corneal thickness

increase in thickness. This increase in CCT in diabetes was interpreted as a minimal corneal swelling and could be the earliest detected change in diabetics.[18] The accumulation of sorbitol due to increased activation of the polyol pathway resulting in oxidative and osmotic stress to the endothelial cells has been proposed to be the causative factor.[19] This results in decreased functioning of the endothelial cells and subsequent edema. However, Inoue *et al*.[14] and Choo *et al*.[3] found no association between the CCT of diabetics and nondiabetics.

Corneal morphological changes have been further correlated with duration of the disease and the glycemic control. Urban *et al*.[19] studied type 1 diabetic corneas in the age group of 15–34 years, and they found the duration of diabetes to significantly affect ECD and CCT. Anbar *et al*.[20] studied endothelial cell morphology in children with type 1 diabetes. They found an increased CCT and decreased corneal ECD in diabetics that significantly correlated with the duration of diabetes. In our study that evaluated only type 2 DM cornea's, there was no association between corneal ECD and duration.

On evaluating of the mean values of CCT, ECD in patients with DM duration ≤10 years and those with DM duration >10 years, no significant difference was found between the two groups in our study well supported by other studies.[21-23] On the other hand, Lee *et al*.[24] found significantly higher CCT and CV in patients with DM duration >10 years than those with DM duration ≤10 years, without any significant difference in ECD and hexagonality between the two groups.

HbA1c levels are based on glycemic control of an individual over a period of 3 months. Allan Storr-Paulsen *et al*.[17] correlated glycemic status by taking an average of 4 HbA1c tests with an interval of 3 months as a reflection of long term glycemic status and found that HBA1c had no impact on CCT; however, higher HBA1C values were associated with decreased ECD. Módis Jr. *et al*.[16] demonstrated an inverse relationship between corneal ECD and HBA1C in the type 1 diabetic patients. In type 2 diabetic individuals, no significant difference was observed in the evaluated values. This suggested the more vulnerability of the type 1 diabetic corneas. Matsuda *et al*.[25] reported a positive correlation of CCT with the duration of diabetes and negative correlation of corneal ECD with HbA1C. Busted *et al*.[18] documented the positive association of HbA1c with CCT. In our study, CCT correlated positively with the duration of disease and only a weak correlation was found with HbA1c. However, there was no such correlation between HbA1C and corneal ECD. The absence of correlation between HbA1c levels and corneal endothelial parameters suggest that these parameters may not be related to short-term glycemic control. Inoue *et al*. claim that although they did not show the influence of duration on the morphology of the corneal endothelium, the relation may not occur during the examination, but it may appear some years later. It has been proposed that in a chronic disease such as DM, subtle changes could develop over a long period of time.[26] Corneal endothelial cell alterations may not correlate to HbA1c measured at one point of time. These findings may suggest the possibility of insult to the endothelium at any time during the course of the disease due to the fluctuating high blood sugars, resulting in a permanent damage to the endothelial cells. This could be one of the reasons for the absence of correlation with duration of the disease and glycemic status. Endothelial cells of diabetic corneas are always at risk of damage as most often blood sugars are only controlled at intermittent intervals by the diabetics. Specular microscopic examination of the cornea should be a regular preoperative investigation in diabetic patients undergoing intraocular surgery even though the blood sugars are well controlled at the time of surgery.[12]

CONCLUSION

Type 2 DM corneas have decreased CECD and increased CCT. Neither duration nor glycemic controls affects the alterations in the corneal endothelial cells. CCT correlates positively with duration of DM.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Awareness and practice toward refractive error correction methods among dental undergraduate students in a tertiary care center in Navi Mumbai

ABSTRACT

Context: Visual impairment is one of the major health-care problems in the world. People pursuing higher education with long hours of studies and excessive near work are more prone to develop refractive error causing visual impairment. Dental students come into this category. In this study, we are trying to evaluate the level of awareness and practices of dental undergraduates toward refractive errors. **Aim:** The aim of the study was to assess the level of awareness and various practices toward refractive error correction methods among dental undergraduate students of a tertiary care center in Navi Mumbai. **Settings and Design:** A cross-sectional study was done by recruiting dental undergraduate students as the subjects, after obtaining ethical approval from the institute and informed consent from the students. **Subjects and Methods:** A random sample of 198 undergraduate dental students were surveyed by a questionnaire. A similar study was conducted in the Goan population, and the questionnaire was taken from that study. **Statistical Analysis:** Statistical Package for the Social Sciences (SPSS v 21.0, International Business Machines (IBM)) was used for the statistical analysis. **Results:** Of 198, a total of 165 students, 58 males (35.15%) and 107 females (64.84%), had got their eyes examined. It was found that 135 students (68.2%) knew the difference between ophthalmologist and optometrist. Females have more usage of spectacles. The use of glasses was maximum among the students with family income >180,000/annum. Around 82 (41.4%) students using spectacles noticed that the use of glasses causes limiting effects on their activities. Hundred and four students were aware of the refractive surgeries. There was a statistically significant difference seen about the awareness between students having annual income <30,000 and >180,000/annum ($P < 0.05$), and 111 students knew about the side effects of refractive surgery. **Conclusion:** There is a lack of knowledge about refractive errors among dental students. It is important to create awareness among them and thereby in the society.

Keywords: Awareness and practices, dental undergraduates, refractive errors

INTRODUCTION

Visual impairment is one of the major health-care problems in the world. The most common visual impairment is caused due to refractive errors. There are different types of refractive errors such as myopia, hypermetropia, and astigmatism. In emmetropia, parallel rays of light coming from infinity are focused on the retina, causing the formation of a sharp image with accommodation at rest. When these rays of light are focused in front of the retina, it is called myopia, and when these rays are focused behind the retina, it is called hypermetropia. Astigmatism is a type of refractive error where refraction varies in different meridians.

Various studies on the prevalence of refractive errors among medical students were done which showed that in Pakistan,

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the prevalence was 58%, Norway: 50%, Copenhagen: 50.3%, Turkey: 32.9%, Singapore 90%, China 71%, and in Western India, it was 45%.[1]

Uncorrected refractive error is the second most common cause of blindness globally, first being cataract.[2] Uncorrected refractive error gives rise to strabismus, amblyopia, etc., Vision is an important indicator of a person's standard and quality of living. To have a better lifestyle and quality of living, it becomes important to treat the vision-related problems. Hence, a good knowledge about the refractive error is necessary.

Refractive error is more common among the students pursuing higher education due to exhausting hours of studies which causes eye strain.[1] Sometimes, refractive errors are asymptomatic, and sometimes, it presents with asthenopic symptoms of headache, blurring of vision, and watering on long hours of studies or near work. Screening and examination should be done carefully in such cases. Apart from having the knowledge about refractive errors, the dental undergraduates should also know about the consequences of uncorrected refractive error and about their treatment options. Different options such as spectacles, contact lenses, and various refractive surgeries are available according to the need and comfort of the individual.

People pursuing higher education with long hours of studies and excessive near work are more prone to develop the refractive error.[1] Dental students come into this category and have to do exhausting hours of studies and near work on dental casts. Thus, awareness about refractive error among them becomes important. In this study, we are trying to evaluate the level of awareness and practices of dental undergraduates toward refractive errors. This would help to give them a correct and better guidance to deal with their refractive problems.

SUBJECTS AND METHODS

Aim

The study aims to assess the level of awareness and various practices toward refractive error correction methods among dental undergraduate students of a tertiary care center in Navi Mumbai.

Objectives

1. To assess the awareness regarding
    a. Difference between an ophthalmologist and an optometrist
    b. Usage and limiting effect of glasses
    c. Use of contact lenses with their associated side effects
    d. Maintenance and hygiene of Contact lens
    e. Awareness of refractive surgery and its side effects.
2. To assess the relationship between various methods of refractive error correction with.
    a. Gender
    b. Financial status.

Inclusion criteria

Undergraduate dental students learning in a tertiary care center in Navi Mumbai were included in the study.

Exclusion criteria

Undergraduate dental students refusing consent for the study were excluded from the study.

Study period

This study was conducted from January 2020 to March 2020 (duration – 3 months).

Study design

A cross-sectional study was done by recruiting dental undergraduate students of a tertiary care center as the subjects, after obtaining ethical approval from the institute and informed consent from the students.

Study sample

The study sample was calculated using the formula, $N = z^2 P (1-p)/d^2$

Study procedure

A random sample of 198 undergraduate dental students who were willing to participate were surveyed by a questionnaire. A similar study was conducted in the Goan population, and the questionnaire was taken from that study.[3] The questionnaire comprised ten questions [Figure 1]. They all were closed-ended questions in the form of Yes/No. All the statistical analyses were done using the IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.

RESULTS

A total of 198 dental students were surveyed, all belonging to the age group of 20–22 years. Of which 72 were male students and 126 were female students [Figure 2]. They were divided into five groups according to their annual income of the parents [Figure 3].

Eye examination and awareness of difference between ophthalmologist and optometrist

Of 198, a total of 165 students have got their eyes examined [Figure 4], in which 58 were male students (35.15%)

Survey Questionnaire

THANK YOU FOR YOUR PARTICIPATION

Age: Gender: Male/Female

Family Annual Income in RM

1) Less than 30,000
2) 30,000 -80,000
3) 80,000 -1,30,000
4) 1, 30,000-1, 80,000
5) 1, 80,000 and above

Q1 Have you ever had an eye examination? Yes / No
Q2 How many times in a year do you get your eye examination done? Once/ twice/ thrice/ four times / more?
Q3 Do you know the difference between an ophthalmologist and an optometrist? Yes / No
Q4 Do you wear glasses? Yes / No
Q5 If yes, do you believe that glasses had limiting effects on your daily life? Yes / No
Q6 Do you aware of contact lens usage instead of spectacles? Yes / No
Q7 Have you ever worn contact lenses? Yes / No
Q8 If yes, Are you aware of possible contact lens side effects? Yes / No
Q9 Are you aware of hygiene and maintenance of Contact lenses?
a. Hand washing before using contact lens: Yes/No
b. Cleaning material: Yes/No

Q10 Are you aware of the possibility of refractive surgery in order to improve the eyesight and decrease or eliminate depending on spectacles? Yes / No
Q11 Are you aware of possible refractive surgery side effects? Yes / No

Figure 1: Survey questionnaire for dental undergraduates

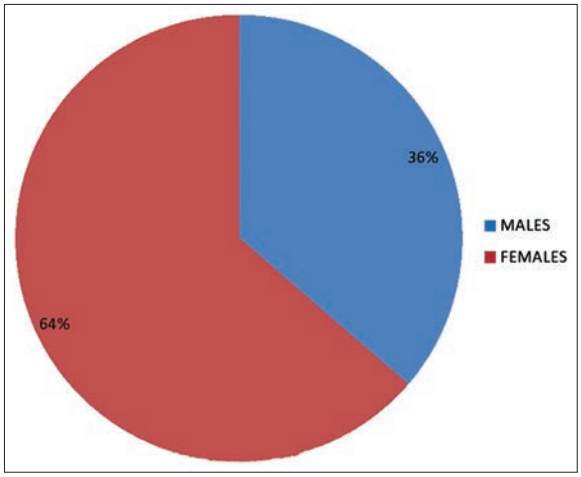


Figure 2: Distribution of the study population as per the gender

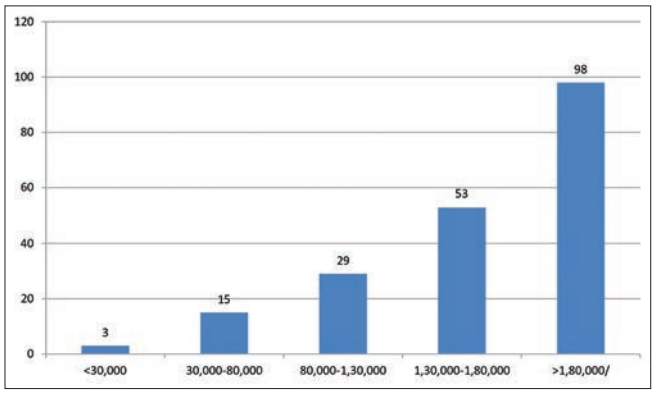


Figure 3: Distribution of the study population as per the annual income

and 107 female students (64.84%), as shown in Figure 5. Females were more cautious and approached the doctor more frequently as compared to males. They came with asthenopic symptoms such as headache, watering, burning sensation, and straining of eyes. It was found that 135 students (68.2%) knew the difference between ophthalmologist and optometrist [Figure 4], of which 90 were female and 45 were male [Figure 5]. It was observed that students with higher annual income were more likely to get their eyes examined at least once in their lifetime. Amongst the students who had got their eyes examined, a statistically significant difference was seen between the students having annual income <30,000 and > 180,000 ($P < 0.01, 0.05$) as shown in Figure 6.

It was noted that students got their eyes examined mostly twice a year, and the frequency of examination was more in students with an income above 180,000 [Figure 6].

Usage of glasses and its limiting effects

A total of 104 students were using spectacles to correct their refractive error [Figure 4], included 35 male (33.6%) and 69 female students (66.24%), as shown in Figure 5. Besides this, the use of glasses was maximum among the students with family income >180,000/annum [Figure 6]. There was a statistically nonsignificant difference seen for the frequencies between the groups ($P > 0.05$). Around 82 (41.4%) students using spectacles noticed that the use of glasses causes limiting effects on their activities such as swimming, having a bath, and watching a three-dimensional movie [Figure 4]. It was more common among female students [Figure 5] and those having family annual income >180,000 [Figure 6].

Awareness of the use of contact lenses, its side effects, and its maintenance and hygiene

It was seen that a total of 42 students [Figure 4], 13 male students (30.95%) and 29 female students (69.04%), were aware of the use of contact lenses instead of spectacles [Figure 5]. Knowledge was maximum among the students with family income >180,000/annum [Figure 6]. There was a statistically nonsignificant difference seen for the frequencies between the groups ($P > 0.05$). All these 42 students aware of contact lenses knew about its side effects and maintenance and hygiene [Figure 4].

Awareness of refractive surgery and its side effects

One hundred and four students were aware of the refractive surgeries being done for correction of various refractive errors [Figure 4], of which 39 (37.5%) were male students and 65 (62.5%) were female students [Figure 5]. Students with parents having family income >180,000 were mostly aware of it [Figure 6]. There was a statistically significant difference seen about the awareness between students having annual income <30,000 and >180,000/annum ($P < 0.05$), as shown in Figure 6. It was observed that 111 students knew about the side effects of refractive surgery [Figure 4], of which 36

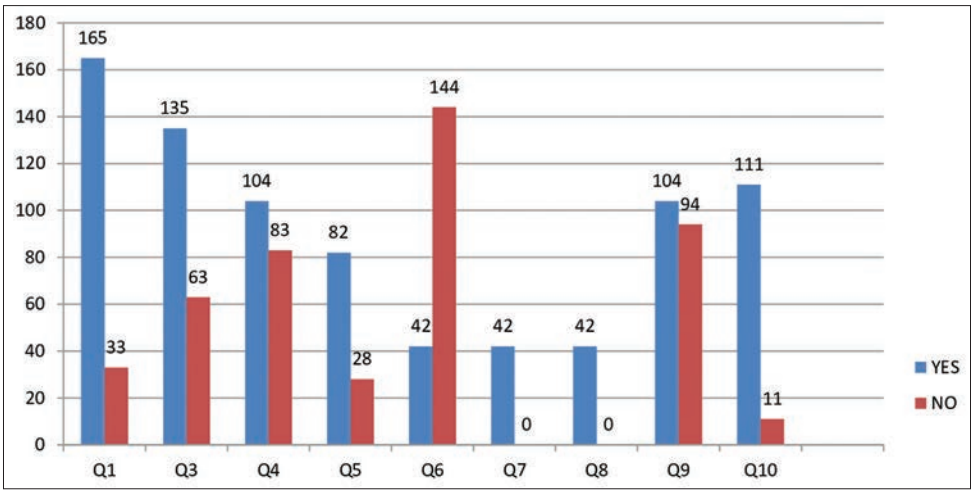


Figure 4: Response of the study population to all questions

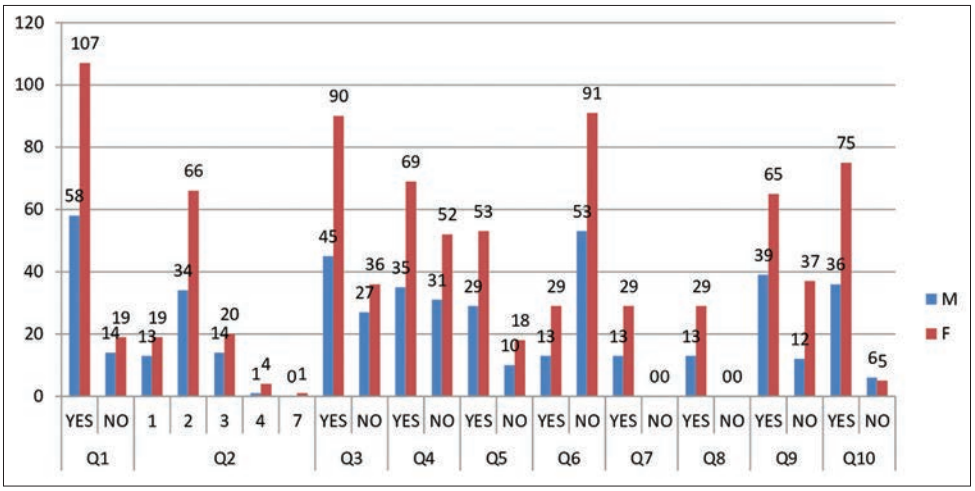


Figure 5: Response of the study population as per the gender

were male students and 75 were female students [Figure 5], in which maximum of them had family income >180,000/ annum [Figure 6].

DISCUSSION

According to the WHO, visual impairment due to uncorrected refractive error is seen in 200–250 million population.[4] Hyperopia (spherical equivalent of + 2.00 and higher) is the main refractive error seen in children of 4–6 years of age.[5] As the age increases, myopia becomes more common, especially in adolescents and young adults.[4] After the age of 40–45 years, presbyopia comes into the picture. Children fail, adults cannot work efficiently, and the elderly population cannot do their day-to-day activities due to uncorrected refractive errors. Thus, refractive error is seen in all age groups.

In this study, we have tried to know the overall knowledge about the common ophthalmic treatment modalities among the dental students. It is just a survey to create awareness on the whole among dental students and note the areas where it is necessary to educate them more. Dental students being future doctors might be asked by the general public about certain basic questions related to ophthalmology. Hence, it becomes important for them to know about it for themselves and the society. This would help to deal with the common public health issue of uncorrected refractive error. It is a sad to note only 68% of the students know the difference between ophthalmologist and optometrist. We also concluded that knowledge varies with socioeconomic status of the family of dental students. Students belonging to a higher socioeconomic status were more aware about the treatment modalities and were also getting routine checkups done. Thus, the economy plays an important role in the quality of life and standard of living. There are students who consider that glasses have a limiting effect on their daily life. This turns out to be one of the major reasons for noncompliance. Unaware of the consequences of not using

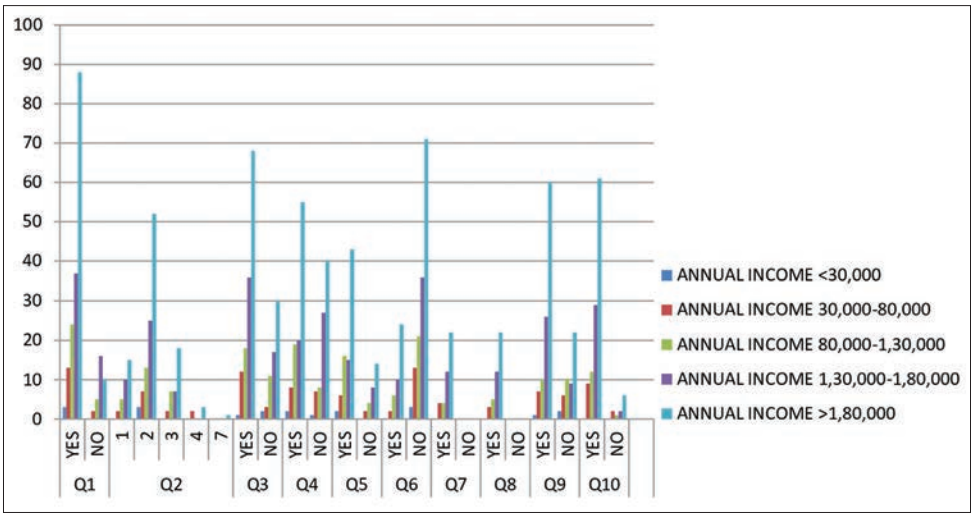


Figure 6: Response of the study population as per the annual income

it and having zero ideas about the other options available further restrict the use of glasses.

Dental students do a lot of fine work in a small area (oral cavity) with a small amount of light actually reaching in the cavity. Good depth perception and clarity in work make their work easier and give better results. If their own refractive error remains uncorrected, the ease and accuracy in work decrease. Thus, it is important for dental students to have a better awareness of refractive error to not only create awareness in the society but also increase their own efficiency at work.

Agrawal *et al*. studied 432 dental students and found that the prevalence of refractive error among the dental students was 64.81%, which included 76 (27.14%) male students and 204 (72.85%) female students. Myopia was the most common refractive error seen among them. The incidence of myopia was found to be 70.4% among the dental population surveyed.[1]

It is also seen that parents tend to delay routine ophthalmic checkups of their children as they are not aware of refractive errors and its consequences. Children frequently visit dentists, especially during exfoliation, can serve as a platform to create awareness among the parents and the children about ophthalmic checkup. Along with their dental camps, a small talk on refractive errors, their symptoms, and importance of its correction can help to create awareness. To bring these strategies into action, it is important that dental students have a basic knowledge about the refractive error.

Usgaonkar and Tambe concluded that of 200, 75% of the participants knew about the difference between an "ophthalmologist" and "optometrist." Fifty-nine percent were unaware of contact lens use, 77.5% about cosmetic contact lenses, and 62% about the side effects of contact lenses. Sixty-four percent of the participants were not aware of the refractive surgeries done for improvement in vision and decreasing spectacle dependency. Twelve percent were aware of the side effects of refractive surgery.[3]

Aldebasi noticed that of 2039, 8% of the study population wore spectacle. Only two-third of the population knew the importance of spectacles. Intellect was the determining factor in how people consider optical correction (21% of basic intellectual background thought that it was important to wear glasses against some 40% of higher intellect). People with higher education are more aware of the visual symptoms that need care (37% against only 26%), presbyopia condition (23% against 11%), an urgency to seek eye care (85% against 29%), and factors aggravating refractive errors in children (45% against 29%). Knowledge about the different forms of optical correction showed a higher preference for spectacles against both contact lenses and refractive surgery.[4]

With this survey, we aim to enlighten dental undergraduates with the knowledge of all the different modalities available for the treatment of uncorrected refractive errors. It also aims to educate them about the advantages and disadvantages of various vision improving methods so that more people can be reached and the health-care system can improve. It is thus crucial to use this statistics for the betterment in future.

CONCLUSION

We have noticed in this survey that there are a lot of loopholes in the knowledge about refractive errors and

its correction options among the dental undergraduate students. It is thus important for the ophthalmologist and optometrist to create more awareness among the dental students about the same by arranging more eye camps and adding new strategies to decrease the burden of uncorrected refractive errors among the dental undergraduates and the society.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Basaloid squamous cell carcinoma of eyelid: A rare presentation in rural India

ABSTRACT

Basaloid squamous cell carcinoma (BSCC) is an aggressive rare sub-variant of squamous cell carcinoma that usually affects the upper aerodigestive tract. Ophthalmic presentation of this variety is rather rare. In our case report, we report a case of primary lower eyelid BSCC, which was treated successfully.

Keywords: Basaloid squamous cell carcinoma, eyelid malignancy, eyelid reconstruction, periocular malignancy

INTRODUCTION

Basaloid squamous cell carcinoma (BSCC) is a rare and an aggressive variant of squamous cell carcinoma as reported by Wain *et al*. in 1986. It has a predilection for the upper aerodigestive tract.[1,2] The hallmark of basaloid cell carcinoma is nesting, lobular, and trabecular arrangement of small crowded cells with scanty cytoplasm with hyperchromatic nuclei, the malignant cells display peripheral nuclear palisading, high mitotic activity with comedo necrosis and small cystic spaces with mucinous material. Less commonly affected sites include nose, PNS, external ear, lungs, vulva, vagina, and uterine cervix.[2] Ophthalmic presentation of this



Figure 1: Left lower eyelid basaloid squamous cell carcinoma

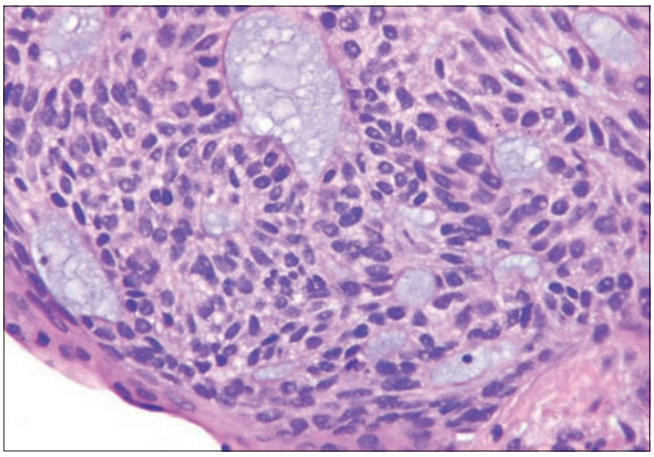


Figure 2: Histopathology of basaloid squamous cell carcinoma

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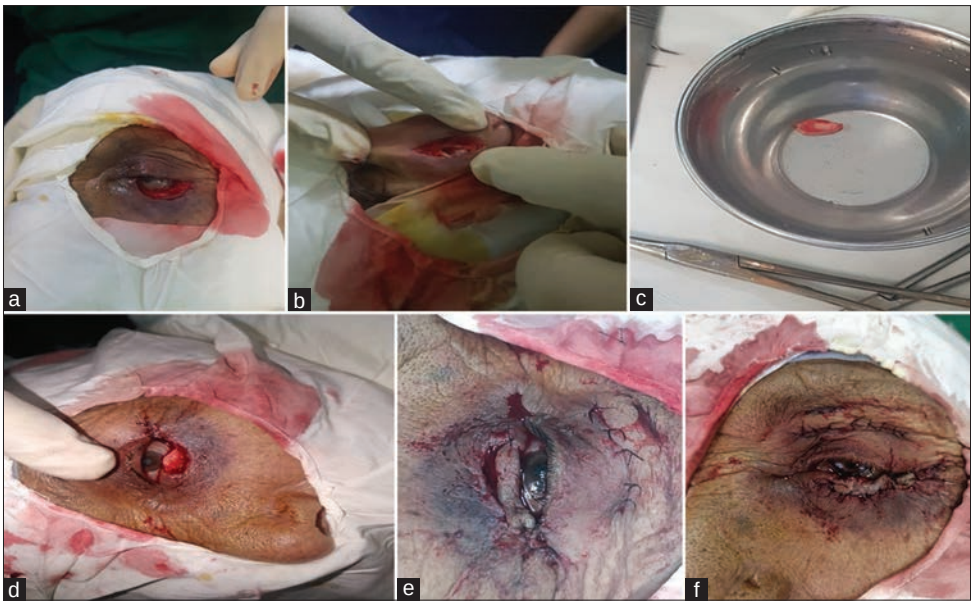


Figure 3: (a) Excision of the lower eyelid lesion. (b) Perichondrial graft procured from the back of the ear. (c) Perichondial graft. (d) Perichondrial graft placement and suturing to lower eyelid excised area. (e) Skin graft from the upper eyelid sutured to the lower eyelid excised area over perichondrial graft. (f) Final picture after completion of suturing

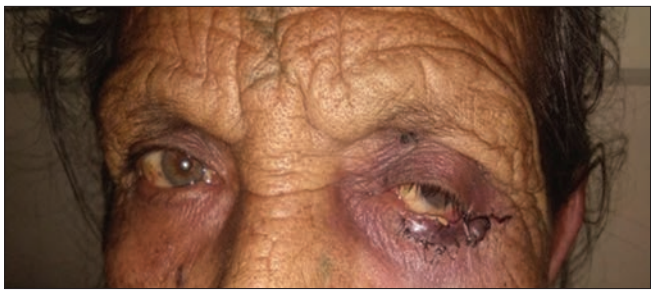


Figure 4: Immediate postoperative picture



Figure 5: (a) Postoperative picture after 1 year. (b) Postoperative picture after 1 year

variant is extremely rare and by far only one case has been reported affecting the conjunctiva. We report a case of BSCC of the lower eyelid which to the best of our knowledge has not yet reported.

CASE REPORT

A 66-year-old female came to the outpatient department with complaints of an ulcerative lesion on the left lower eyelid for 2 years which had gradually increased in size. There was no past history of any ocular trauma, any other debility or fever, addictions, or similar complaints in the family. General and systemic examination was within the normal limits. There were no palpable lymph nodes.

Her visual acuity was 6/36 in the right eye and 6/24 in the left eye with immature senile cataract. On local examination, the lesion was on the left lower eyelid extending from the mid to lateral eyelid measuring about 2 cm × 1.5 cm. It was an ulcerative lesion with an irregular surface and margins [Figure 1], firm consistency, nonpulsatile, and noncompressible. The patient did not complain of pain; however, on palpation, there was mild tenderness. Transillumination was negative, and there was no bruit, with no lymphadenopathy. The rest of the anterior segment was within the normal limits. Fundus examination was within the normal limits. The routine blood investigations showed leukopenia; rest blood investigations were within the normal limits; the chest X-ray was normal. A positron emission tomography (PET) and chest computed tomography (CT) scan could not be performed due to financial constraints.

Surgical management

An incisional biopsy was performed under local anesthesia. The histological examination showed a tumor composed of

polygonal cells with hyperchromatic, pleomorphic nuclei, and scanty cytoplasm separated with fibrous septae with inflammatory cells. There was peripheral palisading pattern of tumor cells. Thus, the histopathological diagnosis was BSCC [Figure 2].

The patient underwent full-thickness excision of the lower lid lesion with clear margins of 3 mm under local anesthesia [Figure 3a]. Margin clearance was confirmed by intraoperative frozen section of the margins of the excised tissue. A perichondrium graft was procured from the back of the left ear of the patient, and a skin graft was taken from the upper left eyelid and grafted over the left lower eyelid [Figure 3b-f]. The grafts were sutured with mersilk 6-0 suture material [Figure 4]. The patient was further referred to our oncology department for further management where she received radiotherapy. The patient was observed for a period of 1 year [Figure 5]. The end cosmetic results were satisfactory, and the lesion has not recurred since then.

DISCUSSION

BSCC affects usually the older age groups mainly individuals from 60 to 70 years. The disease affects men more than the females.[2] It is an aggressive variant of the squamous cell carcinoma which has six times higher risk of distant metastasis and lymph nodal involvement than the former as described by Soriano *et al*.; therefore, a CT chest and PET scan is usually advised to rule out distant metastasis.[3] It is shown to have an association with chronic alcohol and tobacco addiction.[2,3] The most common sites of affection of this rare variant include the base of the tongue, larynx, and hypopharynx. It usually presents as either an obstructive mass or pain. According to the study conducted by Wieneke *et al*., BSCC demonstrated surface dysplasia with no evidence of multifocal disease.[4] In our case, the patient was a female with no addictions, no evidence of pain, and lymphadenopathy with a slow-growing lesion which simulated a basal cell carcinoma. However, the typical histopathological picture labeled it as BSCC.

The eyelid reconstruction is based on the following three main principles: an outer layer of skin, inner layer of mucosa, and a semirigid skeleton interposed between them[5] restoration of eyelid anatomy and function and preventing further spread of the lesion is the main concern of eyelid reconstruction.[6] Performing eyelid reconstruction can be a difficult task as any improper reapproximation can be compromising to the eyelid function and visual function.[7] Utilization of local flaps for lower lid reconstruction has been considered as a gold standard.[8] Skin grafts, free flaps, locoregional flaps, and local flaps are some of the local techniques used for reconstruction.[9] There are various methods for lower eyelid reconstruction described by Barba-Gómez *et al*.[10] Mustarde and the Hughes transposition flap with its modification[11] (4 from NCBI). In our case, we performed a reconstruction of the lower eyelid after complete lesion excision using a perichondrial graft from ear and skin graft from the upper eyelid.

CONCLUSION

BSCC of the lower eyelid is an extremely rare entity as it mainly affects the aero-digestive tract. Proper clinical and histopathological examination can help in the diagnosis. Eyelid reconstruction becomes a very important line of treatment to maintain the integrity of eyelid anatomy and function and prevent further progression the disease.

Declaration of patient consent

The authors certify that they have obtained patient consent form. In the form, the patient has given her consent for her images and other information to be published in the journal. The patient understands that their names and initials will not be disclosed 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

Orbital rhabdomyosarcoma: An atypical presentation

ABSTRACT

Orbital Rhabdomyosarcoma is a lethal malignancy of childhood. It commonly presents in the first decade of life as a rapidly progressive proptosis that can mimic orbital inflammatory disorders. We present a case of a 13-year-old boy who presented with a diffuse right upper lid swelling progressing over 10 days. The detailed evaluation revealed an immobile, firm, and eyelid mass adhering to underlying tissues, not adherent to the skin. The provisional diagnosis of an orbital inflammation was performed. Neuroimaging suggested a preseptal cystic lesion. Intraoperatively, a solid bosselated mass arising from orbicularis oculi, extending into the anterior orbit was excised in toto. Histopathology revealed Stage-1 embryonal rhabdomyosarcoma, confirmed on immunohistochemistry. Postoperatively, the patient underwent systemic chemotherapy. The patient was tumor-free at 2 years follow-up.

Keywords: Embryonal rhabdomyosarcoma, immunohistochemistry, lid swelling, orbital rhabdomyosarcoma

INTRODUCTION

Rhabdomyosarcoma continues to be the most common orbital malignancy in children with a peak incidence between 5 and 10 years.[1,2] It characteristically presents as an unilateral painless proptosis which rapidly progresses to involve conjunctiva, eyelids and can cause secondary changes such as edema and erythema of the lids, conjunctival chemosis, exposure keratopathy, dilated episcleral vessels, retinal detachment, choroidal folds, disc edema, and ultimately causing vision loss.[2,3] It commonly causes abaxial proptosis (80%–100%) with inferonasal globe displacement (80%).[2,4,5]

When the diagnosis is delayed, the 5-year survival rate decreases. However, advancements in chemotherapy have improved prognosis drastically. This has improved the survival rate from 25% to 94% for orbital embryonal rhabdomyosarcomas.[6,7] Meticulous examination, accurate clinical staging, and appropriate protocol based management have improved the outcome of childhood rhabdomyosarcoma.[1,4]

We present a case of embryonal rhabdomyosarcoma in a 13-year-old boy presenting as an acute onset upper eyelid mass.

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CASE REPORT

A 13-year-old boy observed a peanut-sized swelling over his right upper eyelid that progressed over 10 days to involve his entire upper eyelid, causing complete drooping of that eyelid. It was not associated with pain, congestion, or proptosis.

On examination, he had a chin lift but was orthophoric. His best-corrected visual acuity was 20/20 in both eyes (OU) with normal color vision. There was diffuse swelling of the right upper eyelid causing complete mechanical ptosis. A diffuse, ill-defined, firm mass was palpable separate from the overlying skin. It was extending into the orbit superiorly making finger insinuation difficult. The ocular motility of the

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right eye was limited in upgaze. The anterior segment and fundus evaluation were normal.

The other eye examination was normal. He had mild enlargement of bilateral submandibular and contralateral post auricular lymph nodes. The systemic examination was normal.

Computerized tomography scan of the orbit and brain revealed a well-defined hypodense lesion in the preseptal region with post septal extension into the superior orbit, molding around the eyeball [Figure 1]. Ultrasonography of the neck revealed right-sided subcentimetric lymphadenopathy of Level I and Level II neck lymph nodes.

Using a subbrow approach anterior orbitotomy was performed. After meticulous dissection, the mass was excised in toto. Intraoperatively, it was found to be adherent to both orbicularis oculi and levator palpebrae superioris with minimal extension into the orbit. On gross examination, the mass was solid, bosselated measuring about 33 mm × 27 mm × 24 mm [Figure 2].

Histopathology revealed sheets of atypical round to oval cells with a moderate amount of cytoplasm, hyperchromatic nuclei, and a few atypical mitotic figures. Myxoid stroma with few muscle fibers was noted on H and E staining. On immunohistochemistry, the neoplastic cells were positive for cytokeratin, desmin, myogenin, CD 99 and S100, and negative for leukocyte common antigen. It was confirmed as embryonal rhabdomyosarcoma [Figure 3].

The patient had a Group 1, Stage I of orbital rhabdomyosarcoma, and received 12 cycles of adjuvant chemotherapy with vincristine, actinomycin, and cyclophosphamide according to the Children's Oncology Group Protocol (ARST0331) under clinical Group 1. He tolerated the chemotherapy well with minimal systemic toxicity. There has been no recurrence at 24 months of follow-up.

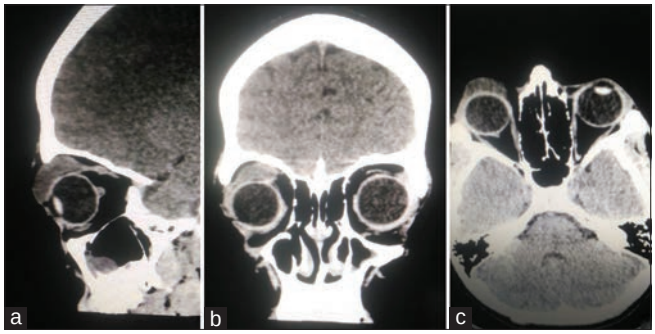


Figure 1: Computed tomography scan of the brain and orbit: (a) Sagittal section (b) Coronal section and (c) Axial section showing hypodense lesion predominantly of the upper eyelid with postseptal extension into the superior orbit, lesion molding along the contour of the globe

DISCUSSION

Rhabdomyosarcoma develops from pluripotent mesenchymal elements, with 45% from the head-and-neck region, 40% from the trunk, 15% from extremities, and up to 10% originating from the orbit.[1,2,4] It is the most common childhood primary orbital malignancy, commonly occupying the extraconal space (40%–80%).[4,5] Almost all cases have proptosis, but our patient had a lid mass. In literature, there are few reports of rhabdomyosarcoma presenting as a lid mass, given in Table 1.[5-12] Rhabdomyosarcoma is known to occur with familial syndromes, thereby suggesting a genetic contribution.[4]

The mean age of presentation is 8 years.[3] The age of presentation of predominantly lid lesions parallels those of orbital lesions.[5-8] Oldest reported case of rhabdomyosarcoma of the orbit 78 years of age.[3] However, in very young children, these eyelid tumors were wrongly diagnosed as vascular malformations leading to delayed diagnosis and poorer outcomes.[6-8] Factors such as early diagnosis and treatment, pleomorphic cell types, and younger age positively influenced outcomes even in eyelid tumors like their orbital counterparts.[6-8]

The five major histopathological variants are as follows embryonal, alveolar, botryoid embryonal, spindle cell embryonal, and anaplastic.[2,3] Favorable prognosis is seen with pleomorphic type attributed to its well-differentiated nature followed by embryonal type, with alveolar histotype holding the worst prognosis.[4] Our patient had an embryonal histotype.

Recommended immunohistochemical panels for rhabdomyosarcoma are desmin, myogenin, myoglobin, and muscle-specific actin. Desmin and vimentin can be indicative but not specific to rhabdomyosarcoma.

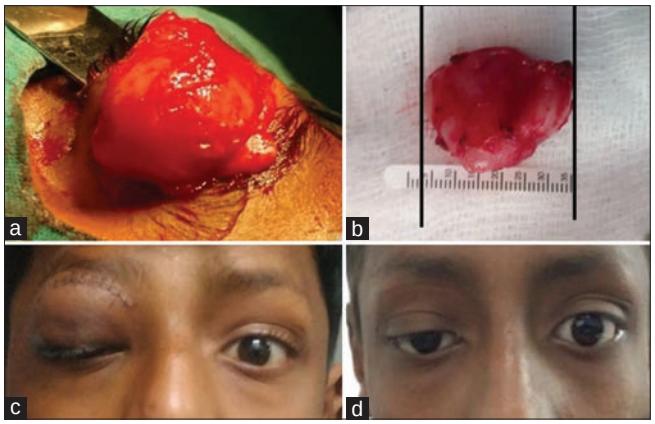


Figure 2: Intraoperatively (a) Mass excised in toto. (b) The dimension of the mass. Clinical picture (c) Immediate postoperative image and (d) One-year follow-up after adjuvant chemotherapy with no signs of local recurrence

Table 1: Lid as a presenting site for rhabdomyosarcoma

Study	Lid rhabdomyosarcoma	Total number of patients	Outcome
Calhoun and Reese; 1942	4	19	Recurrence - 3 Stable - 2 Died - 6 Metastasis - 5 Untraceable - 8
Jones *et al*., 1965	12	62	Stable - 30 Recurrence - 7 Died - 25
Ashton *et al*., 1965	12	34	Stable - 8 Recurrence - 5 Died - 16 Untraceable - 5
Schuster *et al*., 1972	2	2	Stable - 1 Died - 1
Shield's *et al*., 2003	1	30	Recurrence - 6 Stable - 24 Died - 1 Metastasis - 2
Kaliaperumal *et al*., 2007	1	6	Stable - 5 Recurrence - 1
Sharifi *et al*., 2013	1	1	Stable
Lee *et al*., 2016	1	1	Died Metastasis
Essafi *et al*., 2018	1	1	Stable

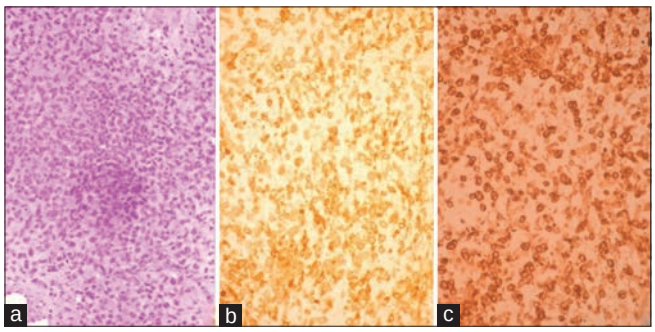


Figure 3: Histopathology (a) H and E Staining showing sheets of atypical round to oval cells with hyperchromatic nuclei and atypical mitotic figures in the myxoid stroma with few muscle fibers. (b) Immunohistochemistry showing CD99 positive staining (c) Immunohistochemistry showing desmin positive staining

Alveolar type predominantly express myogenin (90%).[4,13] Immunohistochemistry in our case showed cytokeratin, desmin, and myogenin positivity.

The North American Intergroup Rhabdomyosarcoma Study Group (IRSG) staged orbital rhabdomyosarcoma.[14] This classification guides the management, grouping, and prognosis of the tumor.[2,4,14] Management guidelines are provided by (IRSG) and by the International Society of Pediatric Oncology Malignant Mesenchymal Tumor as given in Table 2. Our patient had a localized disease that was completely resected.

Management guidelines are provided by (IRSG) and by the International Society of Pediatric Oncology Malignant Mesenchymal Tumor. A combined multimodal approach is applied for the treatment of rhabdomyosarcoma, including surgery, radiotherapy, and stage-based chemotherapy.[1,2,4,6] Radiation is provided in the range of 3600–5040 cGy over 4–5 weeks.[2,4,14]

The favorable prognostic factors include completely resected tumor with tumor-free margin, pleomorphic histology, orbital origin, and tumor size <5 cm.[1-3] About 17% can recur at a median duration of 18 months, of which 8% can occur at a distant site and local recurrence in 92%.[2,4,14] The 5-year survival of those with orbital alveolar rhabdomyosarcoma was 74%.[3] and that of embryonal rhabdomyosarcoma was 94%. As per the literature, our patient has a good chance of 5 years of survival due to early diagnosis and management.

In conclusion, the eyelid rhabdomyosarcoma is rare. It can clinically mimick either eyelid or orbital inflammatory swelling. Early diagnosis and protocol-based management improve the prognosis in rhabdomyosarcoma.

Acknowledgment

We would like to thank the Department of Hematology-Oncology, St. John's Medical College, Bangalore, Department of Pathology, St. John's Medical College, Bengaluru.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has

Table 2: Staging and management guidelines according to the North American Intergroup Rhabdomyosarcoma Study Group

Group	Definition	Management
I	Localized disease and completely resected (excisional biopsy)	Chemotherapy only: VA
II	Microscopic disease remaining after biopsy	Combination therapy: chemotherapy (VAC) + Radiotherapy (36 Gy)
III	Gross residual disease remaining after biopsy	Combination therapy: chemotherapy (VAC) + radiotherapy (45 Gy)
IV	Distant metastasis present at the onset	Combination therapy intensive chemotherapy and radiotherapy

V – Vincristine, A – Actinomycin, C – Cyclophosphamide

given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal patient 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

An unusual case of scleral thinning with uveal exposure following pterygium surgery and its management

ABSTRACT

To report unusual cases of acute onset, complete, non-infected, localized scleral thinning with uveal exposure post pterygium excision and how to manage a case. A 32-year-old female presented with complaints of mild irritation of both eyes for 3 months. On examination, she was found to be having nasal pterygium encroaching 2 mm over the cornea. She underwent an uneventful right eye pterygium excision with conjunctival autograft and was given topical antibiotics and steroid eyedrops. On follow up after 2 weeks she was found to have full-thickness scleral thinning at the site of pterygium excision with uveal exposure. Scleral patch graft with amniotic membrane transplantation was done. Scleral thinning and uveal exposure following an uncomplicated pterygium surgery without mitomycin is a rare serious complication.

Keywords: Cornea, mitomycin, pterygium, scleral thinning, scleritis

INTRODUCTION

Pterygium is an abnormal fibrovascular proliferation of the subconjunctival tissue, which encroaches from conjunctiva onto the cornea with symptoms such as irritation and dry eye. Commonly employed surgical techniques for the treatment of pterygium include excision with conjunctival autograft, use of mitomycin C (MMC), and amniotic membrane transplantation (AMT). A 32-year-old female presented with complaints of irritation of both eyes (BE) for 3 months. She had nasal pterygium and underwent an uneventful right eye (RE) pterygium excision with conjunctival autograft. On 2 weeks of follow-up, she presented with localized scleral thinning with uveal exposure. Donor scleral patch graft with AMT was done, which showed complete epithelialization during 3 months of follow-up.

Scleral thinning is a rare complication that can occur commonly with the use of antiproliferative agent MMC[1,2] and the use of beta-irradiation[3] or if sclera is damaged inadvertently during surgery by deep dissection or excessive cauterization.

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CASE REPORT

A 32-year old female presented with complaints of mild irritation of BE for 3 months. On examination, she had visual acuity of 20 / 30 with nasal pterygium in BE. Corneal topography showed astigmatism of 1.57D at 114 degrees in the RE. Schirmer's test I and II were > 15mm. The patient underwent RE nasal pterygium excision with conjunctival autograft. MMC, suture, or glue was not used. On 1-week follow-up, conjunctival graft was *in situ*. Two weeks later, the patient came for routine follow-up with no complaints, and on examination of RE, she had a localized full-thickness scleral thinning with uveal exposure. On slit-lamp examination, scleral thinning was 4 mm × 3 mm in size with well-defined margins

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and the surrounding sclera was not epithelialized. There was no active sclera inflammation surrounding the melt. The lateral border was 3 mm away from the limbus with minimal chemosis [Figure 1a and b]. Dilated fundus evaluation was normal. B scan ultrasonography did not reveal any signs of posterior scleritis. Intraocular pressure by Goldmann applanation tonometry was 12 mmHg. The other eye examination was normal. The patient was referred to rheumatologist for the evaluation of immunosuppression. Systemic steroids were not given as she was asymptomatic without any signs of inflammation and full-thickness scleral melt at the presentation. Bacterial and fungal cultures were sent to rule out infection.

RE donor scleral patch graft was done under subtenon's anesthesia. Intraoperatively, it was striking to note that medial rectus muscle was exactly inserting at the medial border of the scleral melt [Figure 2a]. A square-shaped scleral patch graft was sutured with 10-0 ethilon [Figure 2b] and the amniotic membrane was secured over the scleral graft using fibrin glue [Figure 2c and d].

The patient was started on topical steroid and antibiotic eye drops with lubricants on the first postoperative day. She underwent complete immunological workup and found to be negative for antinuclear antibody, antineutrophil cytoplasmic antibody, and rheumatoid factor. Montoux was negative. Her hemoglobin was 12.2 g%. The erythrocytes sedimentation rate was 63. Thyroid-stimulating hormone (TSH) was 16.54 and antithyroid peroxidase antibodies (anti-TPO) were >1300; both were elevated suggesting autoimmune thyroiditis but the patient was clinically asymptomatic. The patient had hypothyroidism and was on thyroxine supplementation.

The patient was serially followed up with steroid and antibiotic eye drops. She gradually improved with good graft apposition [Figure 3a]. At 3 months follow-up, it showed complete epithelialization [Figure 3b].

DISCUSSION

Scleral thinning can occur in various systemic and local conditions such as autoimmune diseases, chronic scleritis, myopic degenerations, local scleral pathologies, scleral injuries, prolonged irradiation, transscleral laser cycloablation, strabismus surgery, deep sclerectomy, overuse of antimetabolites, and excessive use of cautery. Scleral thinning postpterygium surgery is usually associated with the use of MMC, excessive cautery, and bare sclera technique.[4]

To the best of our knowledge, this is an unusual case to be reported of sudden onset postpterygium excision scleral thinning with uveal exposure in an uncomplicated pterygium excision without using mitomycin and without any infection in a clinically normal patient with autoimmune thyroiditis, which to our understanding is a very rare complication. In our case, the patient was very young and her thyroid parameters were elevated such as TSH and anti-TPO, but her other systemic autoimmune workup was negative and no clinical evidence of connective tissue diseases. It was a full-thickness sterile scleral melt with a uveal show, which necessitates immediate surgical interventions to avoid perforation, secondary infection, and rarely endophthalmitis.

The overall incidence of scleral necrosis after pterygium excision has been reported to be 0.2%–4.5%.[5,6] A higher rate of scleral melt Has been linked to bare sclera technique with adjunctive use of MMC or beta irradiation. Ti SE Reported 6 of the 20 cases were quite scleral melt without evidence of autoimmune diseases, but in all of the cases, MMC or beta irradiation was used as an adjunctive agent.[7] Gokhale and Samant reported one case of surgically induced necrotizing scleritis with bare sclera technique in a patient with serological evidence of connective tissue disease.[8]

Few infective etiologies have been implicated in the causation of scleral necrosis and aggravation of sclerokeratitis following

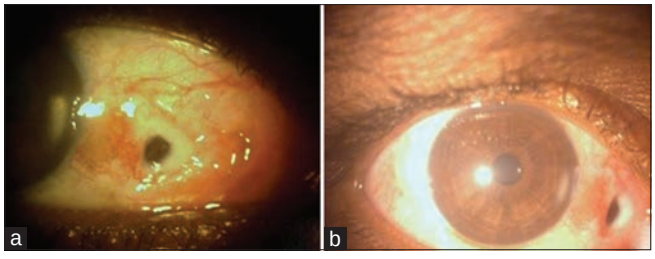


Figure 1: (a and b) Slit-lamp images of patient showing markedly thinned sclera with underlying uveal exposure and mild conjunctival congestion

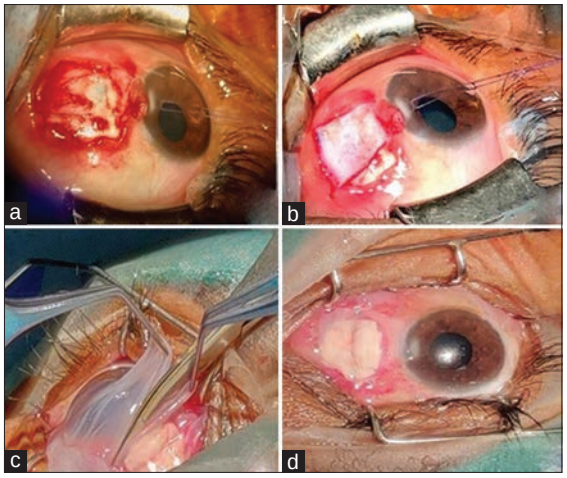


Figure 2: Intraoperative images of patient (a) insertion of medial rectus at medial border of thinning, (b) after placing donor scleral patch graft at the site of perforation. (c and d) Amniotic membrane transplantation over scleral graft

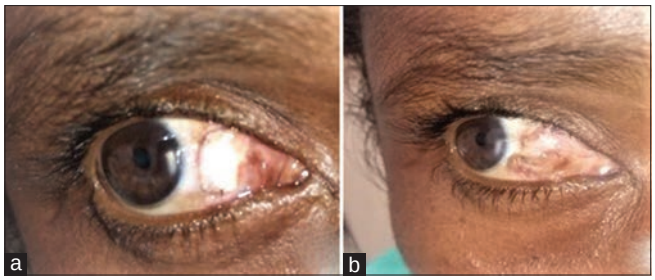


Figure 3: (a) 1 month postoperative image of the patient with graft in place. (b) 3 months postoperative image showing complete epithelialization

pterygium excision.[9] And, the risk is high in patients with autoimmune disease and with the use of mitomycin during pterygium surgery. The use of split-thickness dermal graft also reported in the literature for a corneoscleral defect.[10]

In our patient, surgical trauma or the use of antiproliferative agents were not responsible for the scleral melt. Excessive cauterization might be the cause for scleral thinning which was not noticed intraoperatively. As the patient presented with full-thickness melt, the progression of the thinning was not monitored to rule of surgically induced necrotizing scleritis by giving systemic steroids. Infective scleritis cannot be considered as a differential diagnosis in this case as infective workup was negative. The presence of autoimmune thyroiditis suggests that the patient could be susceptible to immune-mediated reactions. Even the patient is asymptomatic clinically, autoimmune diseases have to be ruled out before taking the patient for any ocular surgery to prevent complications. AMT following scleral patch graft is the best option in such a condition as it helps in epithelialization and healing. Early diagnosis and immediate surgical interventions are successful in managing such complications.

Declaration of patient consent

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

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Conjunctival inclusion cyst presenting as proptosis: A rare scenario

ABSTRACT

Conjunctival inclusion cysts are an uncommon complication following various surgeries. They usually present as cystic masses confined to the anterior segment. We report a case of large inclusion cyst with orbital extension, which presented as proptosis and diplopia.

Keywords: Conjunctival inclusion cyst, scleral buckling, strabismus

INTRODUCTION

Conjunctival inclusion cysts are benign lesions which are lined by stratified squamous nonkeratinizing epithelium, filled with serous fluid and shed cells.[1] They can be either congenital or acquired. Acquired inclusion cysts occur due to implantation of conjunctival epithelium following trauma or surgery or may occur in inflammatory conditions.[2] It has been reported following various surgeries – strabismus surgery,[3] scleral buckling,[4] pars plana vitrectomy,[5] small incision cataract surgery,[6,7] glaucoma valve surgery,[8] and subtenon anesthesia injection.[9]

CASE REPORT

A 54-year-old male presented with protrusion of the right eye, which was painless and gradually progressed over the past 4 years. He also had complaints of double vision. He had undergone scleral buckling surgery in the same eye 10 years back.

On examination, his best-corrected visual acuity was 6/9 (right) and 6/6 (left). The right eye showed gross eccentric proptosis of 30 mm with inferior dystopia [Figure 1]. A cystic swelling (8 mm × 6 mm) was noted beneath the superolateral conjunctiva, which was extending into the superior orbit. All extraocular movements were restricted [Figure 2]; elevation was maximally affected. Fundus examination in the right eye showed the attached retina with buckle effect. Left eye anterior segment examination was within normal limits, and the retina showed prophylactic laser marks.

Computed tomography of the orbit disclosed a cystic, nonenhancing, well-defined mass in the superior orbit with posterior extension, in relation to the buckle [Figure 3 – axial



Figure 1: Gross proptosis with inferior dystopia(right eye)

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cut with an arrow pointing the buckle], displacing the eyeball inferolaterally [Figure 4 – coronal section]. There was no bony erosion.

Orbitotomy was done. A well-defined cystic mass was identified. Clear fluid was drained, and wall biopsy was sent for histopathology examination. It was reported as conjunctival inclusion cyst [Figure 5].

One-month follow-up revealed orthophoric alignment of the eyes [Figure 6], with no extraocular movement restriction [Figure 7]. He had been followed up for 6 months, and there is no recurrence.

DISCUSSION

Conjunctival inclusion cyst can be primary or secondary. Primary may be congenital which occurs due to excessive conjunctival invagination during the embryonic period. Acquired primary cysts occur due to chronic inflammation, wherein the loose epithelium gets implanted into the deeper tissue even with trivial trauma.[10] Secondary cysts develop following trauma or surgery. Conjunctival inclusion cysts occur as an uncommon complication of common surgeries. It is most commonly seen following strabismus surgery and can present even decades after the procedure. Kalantzis *et al*.[11] in a retrospective study described orbital implantation cysts, in which maximum cases were following strabismus surgery, orbital fracture repairs, evisceration/enucleation, and retinal detachment surgery in order.

Majority of the cysts are small, are anterior in location, and are often asymptomatic. But rarely, they can be large with orbital extension producing proptosis, extraocular movement restriction, and compromised cosmesis. One such case following scleral buckling was reported, wherein the patient presented 17 years after the surgery.[8] Garg *et al*. reported conjunctival inclusion cyst which developed 1 year after scleral buckling, but it was confined to the anterior bulbar conjunctiva.[12] Our patient presented to us after 10 years of surgery, but had complaints 6 years after the procedure. Similar clinical presentation had been reported as a complication of hydrogel explants which expanded their own, clinically misdiagnosed as conjunctival cyst.[13] Treatment includes simple surgical excision, or with modifications such as injecting trypan blue and methylcellulose,[14] intralesional injection of trichloroacetic acid,[10] aspiration, and sclerotherapy.[15]

Our case report enlightens the occurrence of inclusion cyst as an uncommon complication of many ocular surgeries and that it can have varied presentations.

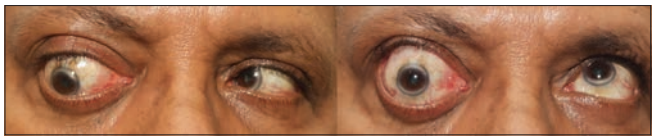


Figure 2: Severe restriction of abduction and elevation

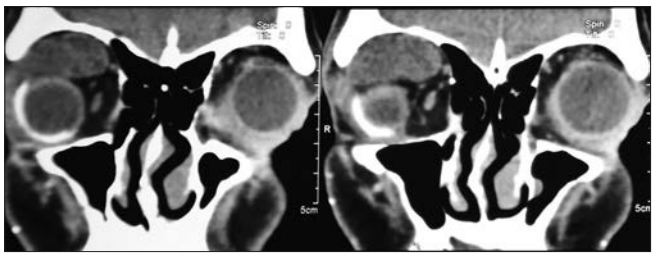


Figure 4: CT Orbit-Coronal sections



Figure 6: Postoperatively,proptosis and dystopia corrected

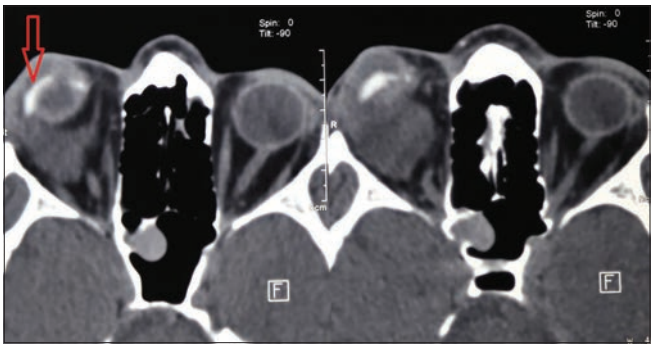


Figure 3: Axial sections of CT orbit (arrowhead shows buckle)

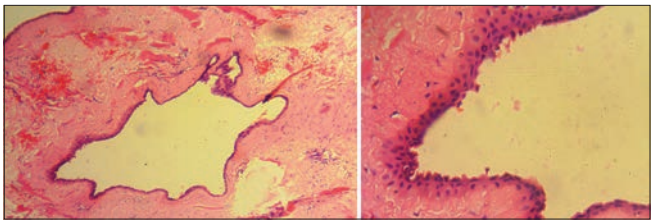


Figure 5: Histopathology - stratified squamous epithelium lined cyst wall

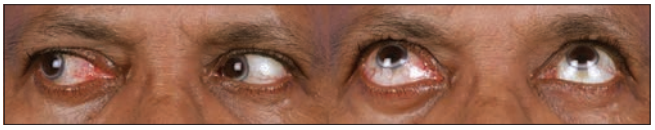


Figure 7: Postop-abduction and elevation resumed completely

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 rare case of osseous metaplasia of an eyelid in a child

ABSTRACT

Osseous metaplasia is the formation of bone within a different tissue. It is a rare phenomenon that occurs primarily in breast tissue and abdominopelvic organs. Intraocular osseous metaplasia is also common. Osseous metaplasia in eyelid is rare entity. We present the case of osseous metaplasia of eyelid in a 6-year-old child. This is the first case of osseous metaplasia occurring in the pediatric population. This case also highlights the importance of coordination between ophthalmologist and pediatrician to obtain relevant history, perform imaging, and hematological test to rule out primary and secondary causes of such swellings to reach accurate diagnosis.

Keywords: Calcification, eyelid mass, metaplasia, pilomixotroma

INTRODUCTION

Osseous metaplasia is the formation of benign bone in abnormal location. It is not applicable to the persistence of embryonic or fetal bone, resulting in calcification or ossification. It is also known as heterotopic bone formation, found in variety of tissue types such as prostate, uterus, breast, skin appendages, pulmonary system, and gastrointestinal organs. Osseous metaplasia in the eye has been reported in few cases till date. Following is the case of osseous metaplasia in eyelid in a pediatric age group.

CASE REPORT

A 6-year-old female child presented to the outpatient department of a pediatric tertiary care hospital with a history of painless swelling in the left eye over lateral canthus for 2 years, gradually increasing in size. It was not associated with any discharge or redness. There was no history of trauma or surgery. Ophthalmic examination of the left eye showed pedunculated mass over lateral canthus of size approximately 0.5 cm, nontender, overlying skin normal, firm in consistency [Figure 1] The rest of the anterior and posterior segment examination of both the eyes was within the normal limits. On cycloplegic refraction, the child was emmetropic. The provisional clinical diagnosis of sebaceous cyst was thought of. Surgical excision of mass under general anaesthesia was planned. Mass was excised in toto, underlying lid margin appeared healthy, and the wound was sutured.

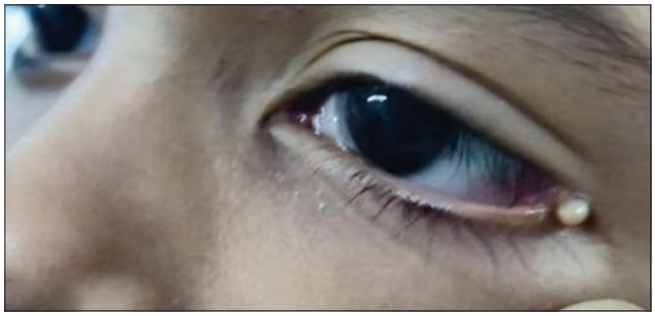


Figure 1: Clinical picture showing a soft-tissue mass on lateral cantus of the left eye

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Figure 2: (a) Scanner view of the mass showing ossified bone beneath the epithelium (H and E, ×40). (b) High-power view showing Haversian system in the bone with overlying unremarkable stratified squamous epithelium (H and E, ×400)

Histopathological examination of the mass revealed ossified bone beneath the stratified squamous epithelium [Figure 2a and 2b]. A diagnosis of osseous metaplasia of eyelid was formed. Child was evaluated extensively to rule out metastasis by conducting hematological and endocrinological profile for any systemic associations to rule out rickets and Albright syndrome. Complete blood count showed increase in acute eosinophilic count. Thyroid profile, rickets profile, and serum electrolytes were within the normal limits. Serum Vitamin D level was 13.63 ng/ml (normal range 30–100 ng/ml). X-ray chest ray pelvic bones, computed tomography abdomen and pelvis was normal. Height of child was between third and tenth percentile, weight was between tenth and 25th percentile for age. Similar growth retardation noted in one sibling. Child was advised Vitamin D supplementation and advised for regular follow-up. The child is in regular follow-up with us, and there is no evidence of recurrence at 6 months of follow-up.

DISCUSSION

Osseous metaplasia is the formation of bone at different location. Causes can be primary or secondary. The primary causes being congenital Albright's hereditary osteodystrophy and progressive osseous heteroplasia. The secondary causes include trauma and chronic inflammation. Chronic inflammation triggers local factors to transform cells into osteoblasts leading to bone formation. Abnormal concentration of calcium phosphorus, PH level, and oxygen concentration can be additive factors.[1,2]

Osseous metaplasia is frequently reported in breast tissue and abdominopelvic organs. Other locations being thyroid[3] and ocular tissue.[4] Vemuganti GK[4] reported intraocular ossification in 8 out of 151 cases, common location being subretinal or preretinal. Pthisis bulbi due to trauma or retinal detachment, staphyloma, microophthalmos was common causes. Although intraocular ossification is common, osseous metaplasia in ocular adnexa is rare. Till date, only 2 cases of eyelid osseous metaplasia had been reported by Liu *et al*.[5] both cases were more than 40 years' age with a history of recurrent trauma to skin. The index case is the first case of osseous metaplasia of eyelid in the pediatric age group. The current case lacks a history of trauma or previous excision plus no definite cause for ossification, leading to idiopathic origin of lesion. The lesion differentiated from pilomixotroma of eyelid, which is common in children by the absence of reddish or bluish appearance of skin. Treatment of choice is complete excision. Systemic evaluation for the presence of any malignancy is necessary. Regular follow-up is needed to check any recurrence.

In conclusion, osseous metaplasia of eyelid is a very rare entity with variety of differential diagnosis. Its importance is highlighted by proper coordination between ophthalmologist and pediatrician to obtain relevant history, perform imaging, and hematological test to rule out primary and secondary causes to reach accurate diagnosis. In Index case, complete excision of the mass lead to eradication with no relapse till date.

Consent

informed and written consent was obtained from parents.

Declaration of patient consent

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

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Photo Essay

Foreign body through the looking glass: Scheimpflug Imaging in inverse contrast

ABSTRACT

A 55-year-old male presented with foreign-body sensation in the left eye, with a history of hammering a chisel. On slit-lamp evaluation, two iron corneal foreign particles with rust ring were noted. The foreign bodies were removed with 26G hypodermic needle after instilling local anesthetic drops. The purpose of this manuscript was to provide a better understanding of the role of Scheimpflug imaging in objective evaluation of corneal epithelialization in such situations. Scheimpflug imaging along with anterior segment optical coherence tomography can be used to support diagnosis, objectively monitor the healing process (epithelialization) after removal, and reveal unexpected lesions, invisible on slit-lamp biomicroscopy.

Keywords: Anterior segment optical coherence tomography, foreign body, Scheimpflug imaging

INTRODUCTION

Patients with corneal foreign bodies (FB) commonly present to emergency departments, urgent care centers, primary care providers, and eye care providers.[1-3] The cornea being the most richly innervated tissue in the body leads to multiple ocular symptoms such as pain, photophobia, decreased vision, copious tearing, blepharospasm, and conjunctival hyperemia, when a FB gets lodged in it.[4] When objects are deeply embedded, corneal scarring or irregularities may occur, resulting in significant visual disruption.

In this report, the role of the Scheimpflug imaging system is highlighted in a situation where multiple FBs were lodged relatively deeper in the cornea. The application of the novel measuring tool, using the calipers of the Scheimpflug imaging system in inverse contrast, is highlighted for accurate mapping of the corneal healing process postremoval of the two relatively deep iron FBs with rust ring.

CASE REPORT

A 55-year-old male presented with foreign-body sensation in the left eye with a history of hammering a chisel. On slit-lamp evaluation, two iron corneal foreign particles with rust ring [Figure 1] were noted in the cornea. As they appeared to be lodged relatively deep in the layers of cornea [Figures 2a and 3a], Seidel's test was done, and it was negative. Scheimpflug imaging [Figures 2a and 3a] also confirmed that the lesion was only partial thickness and did not penetrate the deeper layers. The FBs were then dislodged, and the rust ring was completely removed with 26G hypodermic needle after instilling local anesthetic. After removing the FBs, a final evaluation with fluorescein sodium dye and cobalt blue light was performed with slit-lamp biomicroscopy for documenting the epithelial defect. Broad-spectrum topical antibiotics for 1 week were advised, and the corneal surface reepithelialization was monitored objectively, with Scheimpflug imaging system and anterior

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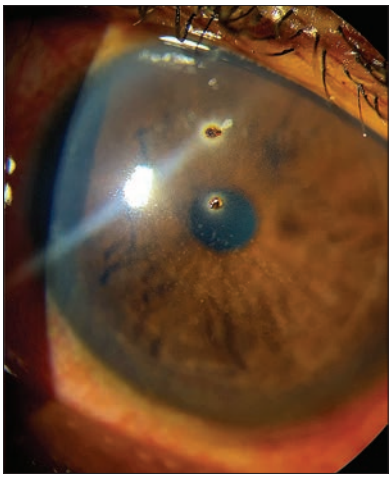


Figure 1: Slit-lamp examination revealing two iron foreign bodies with rust ring

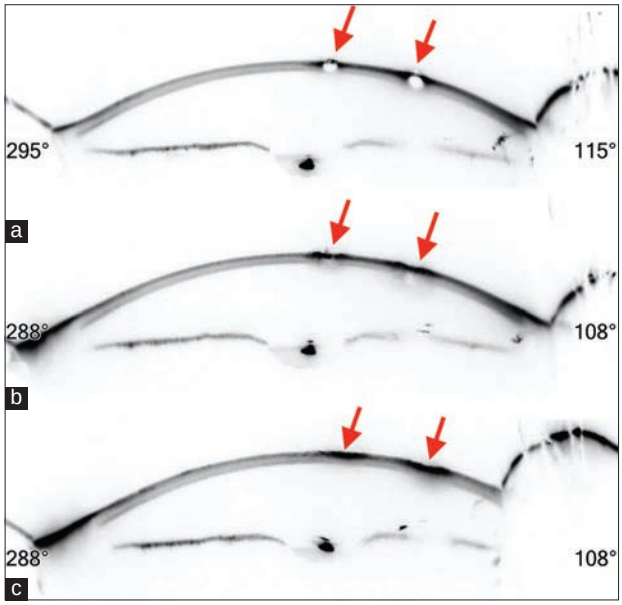


Figure 3: Scheimpflug imaging system in inverse color. (a) Image taken before removal of the foreign bodies (red arrow). (b) Image taken post immediate removal of the foreign bodies showing epithelial defects (red arrow). (c) Image taken 1-day post removal of foreign bodies showing the resolving epithelial defects (red arrow)

segment optical coherence tomography (AS-OCT). Objective revaluation of the cornea was done with Scheimpflug imaging system [Figures 2-6] in inverse contrast with the usage of calipers to assess the depth of the excavation and extent of the epithelial defect in a more precise manner, to monitor, evaluate, and understand the healing process. Scheimpflug imaging was done before the FB removal, immediately after the FB removal, and 24 h after the FB removal.

DISCUSSION

Corneal FBs are the second most common type of ocular injury, comprising approximately 30.8% of ocular injuries.[5]

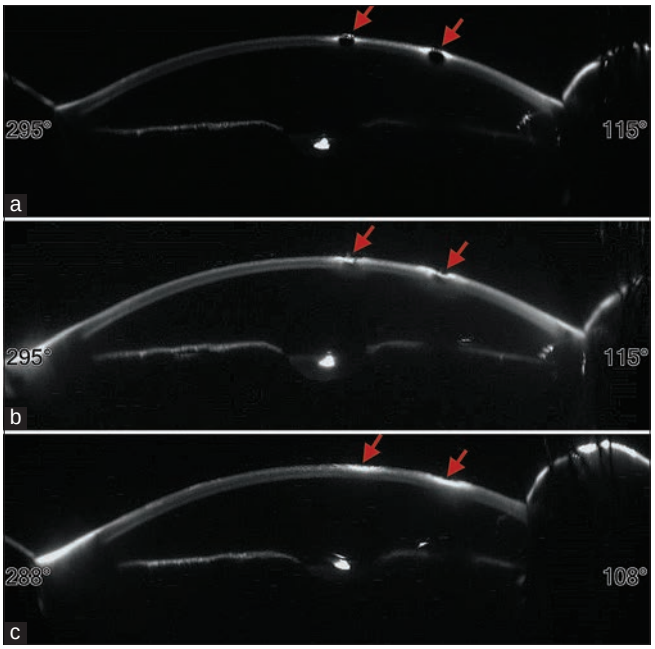


Figure 2: Scheimpflug imaging system. (a) Image taken before removal of the foreign bodies (red arrow). (b) Image taken postimmediate removal of the foreign bodies showing epithelial defects (red arrow). (c) Image taken 1-day postremoval of foreign bodies showing the resolving epithelial defects (red arrow)

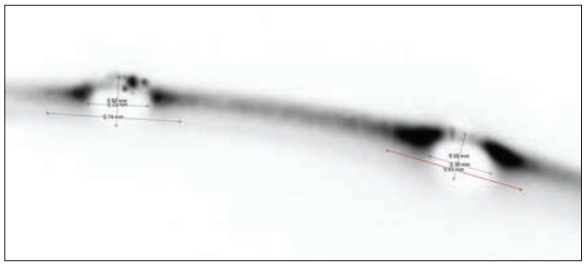


Figure 4: Scheimpflug imaging with calipers measurement measuring the dimensions of the epithelial defect 0.74 mm and 0.83 mm, respectively, with measurements of the white backscattering artifacts (0.33 mm × 0.62 mm and 0.56 mm × 0.38 mm, respectively) from the iron foreign bodies such as foreign body 1 and foreign body 2 before removal

Scheimpflug imaging system along with AS-OCT [Figure 7] can be used to support diagnosis of it, monitor the healing process after removal, and reveal unexpected lesions, invisible on slit-lamp examination.[6-9] To our knowledge, the role of Scheimpflug imaging in objective monitoring of epithelialization postcorneal FB removal is not reported in literature. Scheimpflug imaging (Sirius, CSO, Italy) images the AS of the eye from the front of the cornea to the back of the lens in the coronal plane by capturing the slices through the anterior chamber with high resolution and provides objective documentation of the AS with good three-dimensional corneal assessment in a fast and accurate way.

Usage of Scheimpflug imaging system calipers and inverse contrast for accurate mapping of epithelialization

Scheimpflug system in this patient reveals the foreign body

and the epithelialization postremoval [Figure 2]. With the application of the inverse contrast [Figure 3], the FB, its artifacts, and the epithelialization were appreciated much better and were more distinct than the default picture. Hence, Scheimpflug analysis with calipers was done in the inverse contrast image and high magnification [Figures 4-6]. The dimension of the epithelial defect before removal [Figure 4] was 0.74 mm and 0.83 mm, respectively, with the measurements of the white backscattering artifacts (0.33 mm × 0.62 mm and 0.56 mm × 0.38 mm, respectively) from the iron FBs (FB1 and FB2). Scheimpflug imaging with caliper measurement taken immediately after removal [Figure 5] showed the extent of the abrasion with epithelial defect (1.01 mm and 0.45 mm from FB1 and 1.04 mm and 0.49 mm from FB2, respectively) with the absence of the white backscattering artifacts. Scheimpflug imaging with caliper measurement taken after 24 h postremoval [Figure 6] shows the reduction of the corneal abrasion and epithelial defect (0.94 and 0.46 mm from FB1 and 0.96 mm and 0.48 mm, respectively). The depth of the epithelial defect reduced from 0.19 mm to 0.18 mm in the crater created by FB1 and the depth of the epithelial defect remained 0.16 mm in the crater created by FB2 in the 24 h follow-up [Figures 5 and 6].

The nature and extent of the FB event may determine the course of healing.[10] Small, superficial FB is easily removed with little or no risk of negative sequelae. FBs more deeply embedded, as in this scenario or located centrally, are likely to result in visually significant scarring. An iron foreign body will usually leave a rust embedded in the corneal stroma. Rust can cause inflammatory reaction and delay wound healing and additionally promote scarring with corneal irregularity. However, in our scenario, due to skillful dislodgment of the FB with complete rust removal, the reepithelialization process was almost complete within 24 h postremoval without inflammation [Figure 6].

Although one can argue that these lesions are seen regularly and are visible on the slit-lamp biomicroscopy, the role of Scheimpflug imaging to monitor the epithelialization postremoval in such lesions is warranted to understand the innate nature of corneal healing, which is not objectively possible on a slit lamp with fluorescein staining alone.

CONCLUSION

Our observation suggests that the calipers with Scheimpflug imaging in inverse contrast are available to quantitatively measure the dimensions of reepithelialization during wound healing, post-FB removal. Thus, we conclude that Scheimpflug

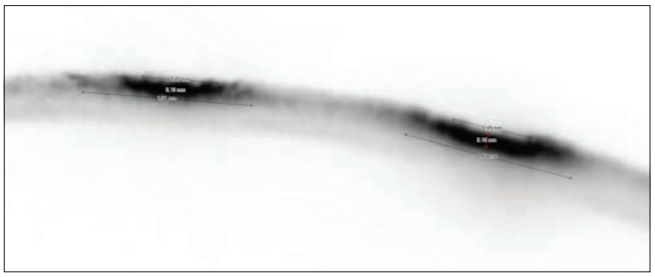


Figure 5: Scheimpflug imaging with calipers measurement immediately after removal showing the extent of the abrasion with epithelial defect (1.01 mm and 0.45 mm from foreign body 1 and 1.04 mm and 0.49 mm from foreign body 2, respectively) with the absence of the white backscattering artifacts. The depth of the epithelial defect craters is 0.19 mm and 0.16 mm created by foreign body 1 and foreign body 2, respectively

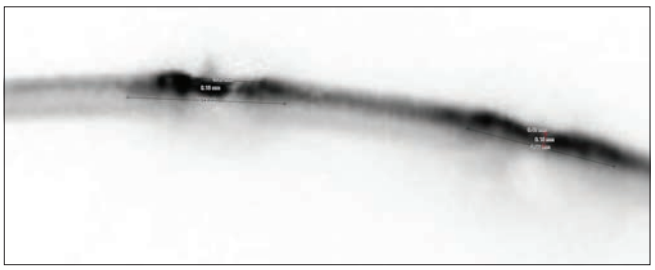


Figure 6: Scheimpflug imaging with calipers measurement taken after 24 h postremoval showing the reduction of the corneal abrasion and epithelial defect (0.94 and 0.46 mm from foreign body 1 and 0.96 mm and 0.48 mm, respectively). The depth of the epithelial defect craters is 0.18 mm and 0.16 mm created by foreign body 1 and foreign body 2, respectively

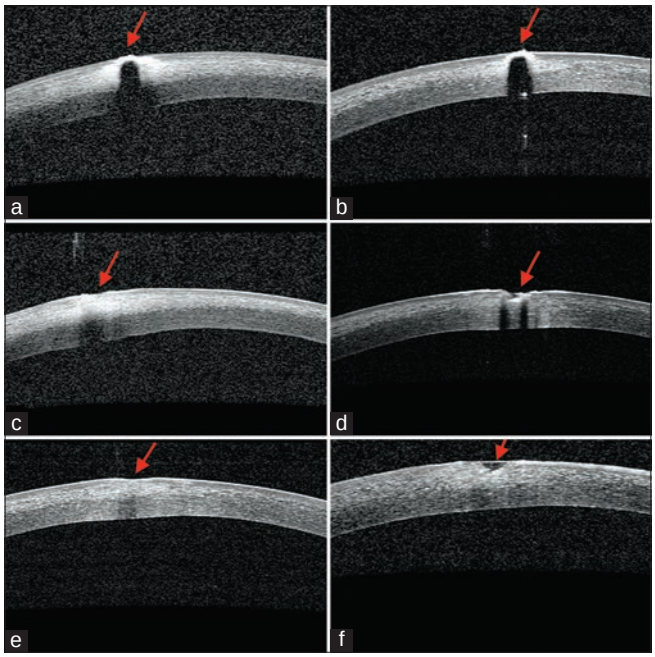


Figure 7: Anterior segment optical coherence tomography. (a and b) Image taken before removal of foreign bodies (foreign body 1 and foreign body 2) revealing both the foreign bodies embedded on the cornea with back shadowing in the deeper layers of the cornea (red arrows). (c and d) Image taken after immediate removal of foreign bodies showing epithelial defect with reduction of the back shadowing (red arrows). (e and f) Imaging taken 1 day after removal showing resolving epithelial defects with epithelialization (red arrows) with the absence of back shadowing

imaging is an extremely helpful imaging tool in monitoring corneal health in relatively deep corneal FBs.

Declaration Of 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 patient understands that names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Innovative utilization of patient's triage with integrated information system during COVID crisis

Circuses often feature risky balancing acts. So do eye care professionals, in the form of wait times especially during COVID crises.[1] A patient's negative experience with wait times in hospitals during this pandemic will have a ripple effect that extends from close friends and family to strangers on the Internet. This innovation will serve as a potential cure for wait time frustration and create the awareness of disease and safety measures during triage wait time.

With the advent of the COVID-19 pandemic, we created an isolation cubicle with acrylic [Figure 1] and shifted all outpatient department (OPD) and investigative tools into it. This measure was done to reduce face to face interactions between the doctor and patient. Furthermore, to minimize patient movement inside the hospital premises, triaging was done in the underground basement car parking area outside the hospital OPD block.[2] Although it was successful in creating a barrier for preventing the virus spread, it also; created a physical barrier between the doctor and patient and communication became quite challenging. Hence, we created this do it yourself workflow tool with rapid and intuitive technology, to gather quantified information from the OPD patients, during their triage wait time and used the same data to make incremental improvements in practice delivery.



Figure 1: The acrylic cubicle inside which all gadgets were integrated with analysis of the information technology displayed on the doctor's personal computer required to evaluate the knowledge of the patient before consultation

We provided specific questionnaires with pictures and WhatsApp educative videos containing items [Figure 2] related to disease knowledge, investigations, management and compliance to the mobile phones of the patients once they have registered and made them answer the Google forms [Figures 3-8] during their waiting time.[3,4] Their knowledge assessment regarding the disease will be done automatically once they have completed the survey. Answering was done during their triage wait time, and results were automatically generated to the doctor's personal computer [Figures 9 and 10] inside the isolation cubicle, so practice delivery can be customised according to the patient's knowledge about the disease process.[5] The patient was also sent to their smart phone, video of the safety precautions [Figure 11] taken inside the hospital to alleviate anxiety regarding transmission of infection and was requested to follow the safety protocols. This tool not only helps patients but also does self-evaluation of our practice pattern itself.

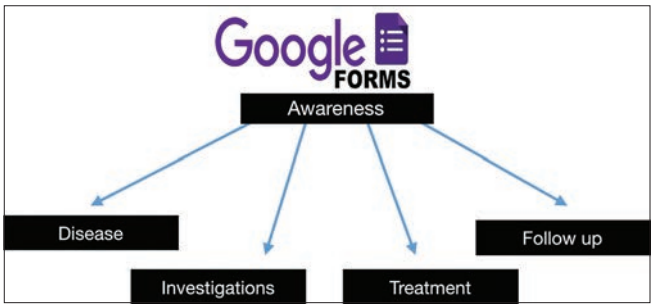


Figure 2: Components of the questionnaire that are though Google forms for evaluation

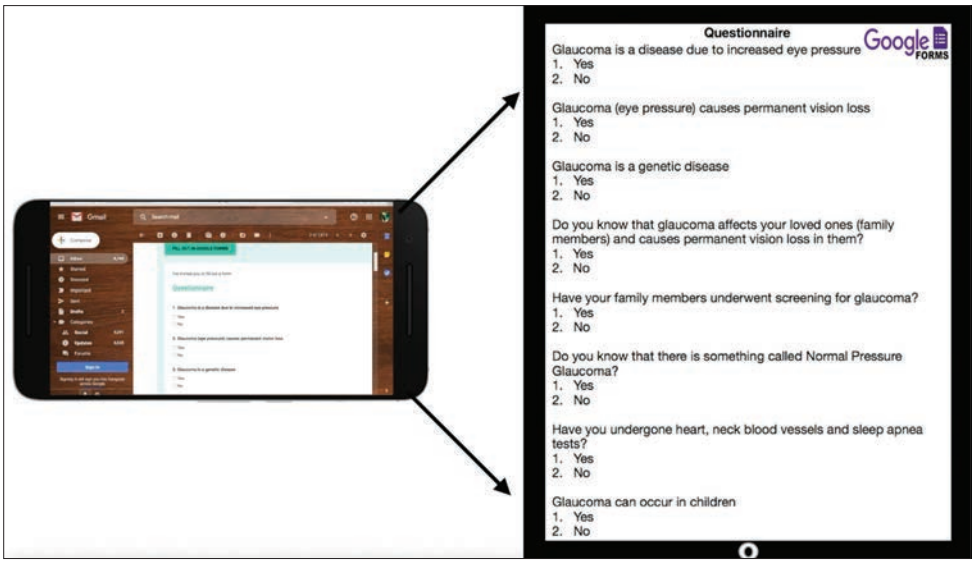


Figure 3: The basic set of questions put forth to a (glaucoma) patient

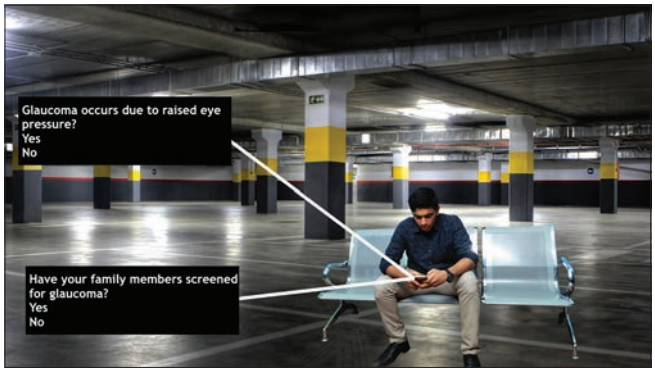


Figure 4: Example of basic questions asked regarding disease awareness

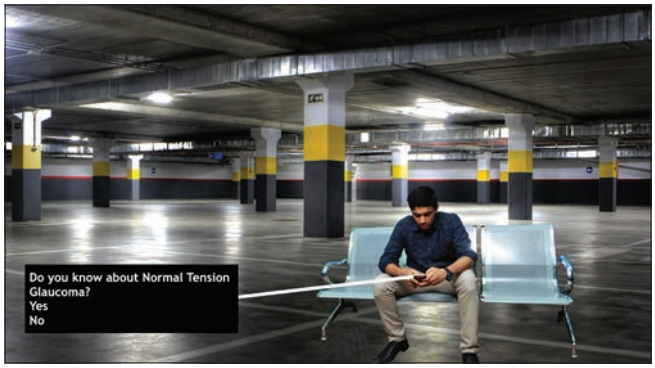


Figure 5: Example of advanced questions asked regarding disease awareness

An additional feature of this tool is; it primes the patients with do's and don'ts for smooth performance, before an investigation [Figure 12] needing patient's co-operation (for example, visual fields) during the wait time. Furthermore, there will be an auto-generated SMS/email to the patient for their next investigation/next review due, highlighting the need to analyze the disease's stability (serving as a vigilant medium).

In this era of smart phones; for 1.3 billion Indian population, there are atleast 1.8 billion mobile phones being used with 92.03 connections per citizen. Among them, roughly half (49.7%) of the mobile phones users are smart phone users. To prevent triage wait time frustration; simultaneous awareness creation and understanding the understood for customised practice delivery, this simple but effective tool will work wonders, needing just a smart phone from the patient's side. Understanding, how much the patient has understood will not only make them feel special and awe of our services but also throw light, in which category we need to strengthen the counselling for that individual, rather than a diffuse briefing that may not yield fruitful results.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

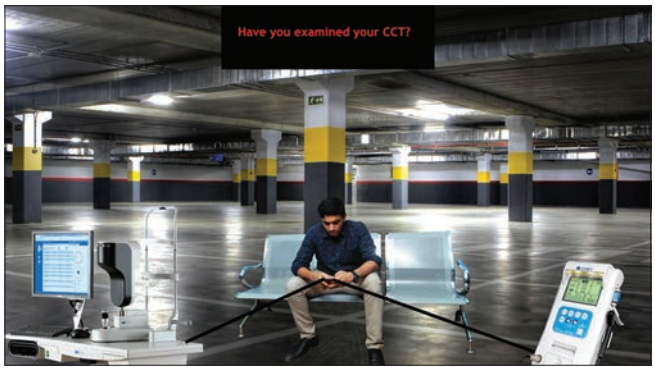


Figure 6: Example of questions asked regarding investigation awareness such as central corneal thickness (CCT), anterior chamber depth (ACD) and lens thickness

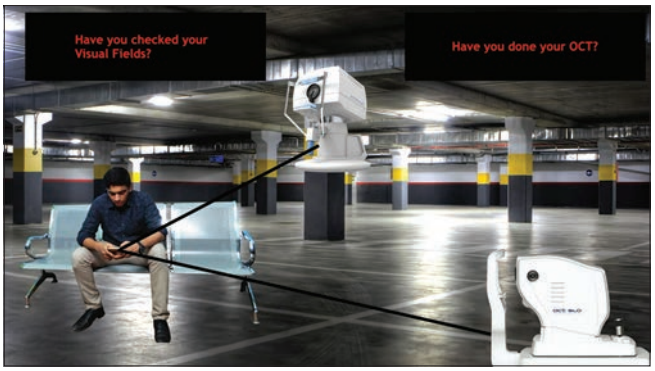


Figure 7: Example of questions asked regarding investigation awareness such as structural evaluation with optical coherence tomography (OCT) and functional evaluation with visual field testing

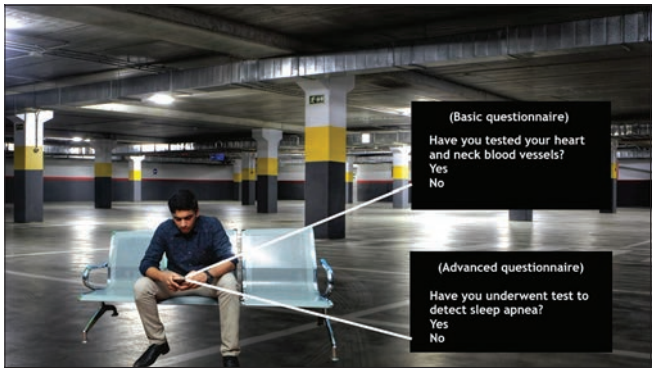


Figure 8: Example of basic and advanced questions asked regarding treatment awareness

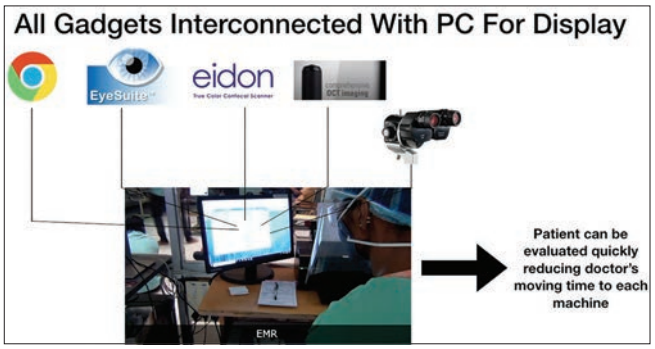


Figure 9: The analysis of the patient's awareness profile is projected on the doctor's personal computer inside the cubicle, which is also simultaneously connected with all investigative gadgets through local access network

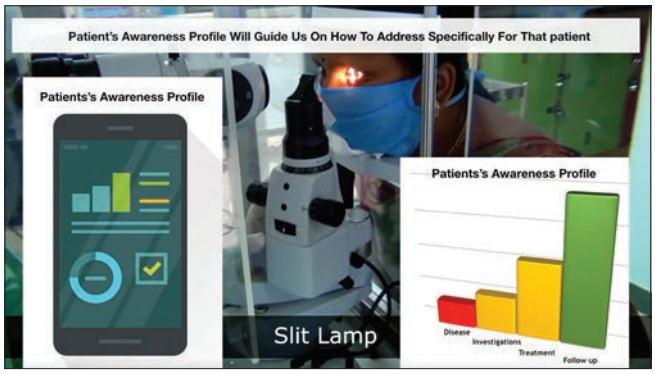


Figure 10: The display of patient's awareness profile available before slit-lamp examination for customizing counseling and practice delivery



Figure 11: Video briefing on the safety measures undertaken inside the hospital premises and investigative instructions sent to the patient's phone during triage wait time for patient's visualisation

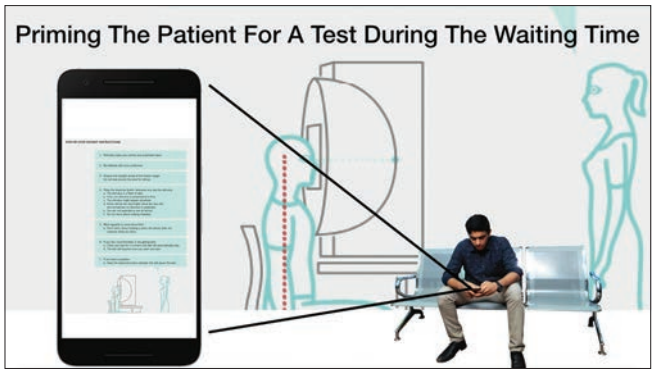


Figure 12: Video briefing on what is expected of the patient during visual field testing sent to the patient's phone during triage wait time for patient's visualization

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The champion runner who became the forerunner in ophthalmic surgery training

The Oxford Room of the Royal College of Ophthalmologists, London, houses the college museum and historical library. There is a mind-boggling collection of antique surgical and optical instruments and books there which can by themselves chart the history of ophthalmology. A good collection of honorary medals and other honors won by great men who shaped European ophthalmology is another attraction. But among that medal collection is one stand out shining piece of metal that is going to surprise the uninformed viewer as it is something which is hardly expected amidst the academic decorations. It is an Olympic Bronze Medal – The 1924 Paris Olympic Bronze medal to be exact [Figure 1] medal.

THE MAKING OF THE OLYMPIAN OPHTHALMOLOGIST

H B Stallard is a familiar name for the ophthalmology resident as his book "Stallard's Eye Surgery" is considered as sort of a bible for the aspiring ophthalmic surgeons. It is highly unlikely that such a book be written again as it was a single author textbook describing almost all the surgical techniques in ophthalmology. Five editions were published from 1946 to 1973 and all the illustrations, perfect in every detail were drawn in pen and ink by the author himself. The book was then revised by Michel Roper Hall, who arranged it in 12 chapters each dealing with one surgical subspecialty.[1] While it was those gifted hands of his, both of which were equally dextrous that earned Stallard a place in the ophthalmic history as a surgeon, writer, and teacher, it was his feet that helped him place an indelible mark in the history books outside ophthalmology. It was only after an intervention from the fate that resulted in a reduction in function of his lower limbs that the upper ones gained an upper hand. What was a loss for Britain's athletics was a gain for world ophthalmology. It requires just one sentence to show how great his achievement in the sports world was. He won the Bronze medal in the 1500 m race in the Paris Olympics representing Great Britain.[2,3] No other ophthalmologist has won an Olympic medal before him or after him.



Figure 1: Both sides of the medal (Reproduced with permission from The Moorfields Collection in the archive of the joint Moorfields and Royal College of Ophthalmologist Library)

Major Hyla Bristow Stallard MBE FRCS who mostly went by the name Henry Stallard was born in Leeds on April 28, 1901, as the eldest of three brothers. He was an excellent athlete and sportsman right from his school days. However, it was from 1919 when he joined the Gonville and Caius College, Cambridge that his athletics career really began to blossom. Henry wanted to become a great middle-distance runner and trained hard for the same. In 1920, his team set a new world record by beating America in the 2 mile Pennsylvania relay. The New York globe headlines read "American Milers must watch Stallard at Antwerp" (Antwerp Olympics). However unfortunately, Stallard had broken his toe in Pennsylvania and so could not be selected for the Olympics that year.[4] In 1922, he graduated and won the Shuter Medical Scholarship to St Bartholomew's Hospital, London. The demanding life of a medical student however did not curb his passion at all. The daytime was entirely devoted to studies and the nights for pursuing his passion. The empty night streets of London became his running tracks. The next 5 years saw Stallard attaining peak athletic proficiency. He became the only athlete in British Amateur Athletics ever to win the mile, the half-mile and the quarter-mile. Naturally, he was chosen to represent Great Britain in the 800 and 1500 m races in the 1924 VIII Olympiad held in Paris.[2] He had even beaten fellow Cambridge runner Douglas Lowe during the trials, who was also selected along with him.

The bittersweet events that unfolded in that Olympics athletics meet and narrated by Hugh Williams are sure to touch the average ophthalmologist's heart.[2,4] HB Stallard was considered favorite to win the 800 m. However, the schedule of the events was such that he had to run on 5 consecutive days as he was there in two events. This took a toll on Stallard's right foot which became known only in the 800 m finals, when despite being in the forefront initially,

he finished in pain as a gallant fourth. The gold medal was won by Douglas Lowe whom he had beaten during the trials [Figure 2]. However, the 1500 m was still there and he was going to compete injury or no injury. Nursing the injury which he thought was minor, he ran the following afternoon for the last 1500 m heats, won, and qualified for the finals scheduled the following day. However, he was in considerable pain and his right foot seemed to be injured badly (a stress fracture and a ruptured ligament as would be discovered later). The team physician examined the foot and said it is better that he withdraws as the foot may not take the stress and might collapse if he runs on that. The team captain also tried his best to dissuade Stallard from running the following day. However, Stallard said adamantly "I am going to run tomorrow even if I never run again"[4] and did exactly that with a bandaged foot. It was the most painful and agonizing race that Stallard ever ran. He came third, just two seconds behind the winner Paavo Nurmi of Finland. He was in terrible pain and collapsed immediately after crossing the finishing line. The unconscious Stallard had to be stretchered off [Figure 3]. The first words of the man who had run the last three races on a fractured metatarsal bone after regaining consciousness were "Sorry Philip for the poor show." Philip Noel Baker was the Captain of Stallard's team. The Olympic Bronze medal thus won by Stallard shone better than the gold medal, for his countrymen and Stallard was welcomed back in his country as a true hero and carried on shoulders. His courageous running in that Olympic event has been immortalized in the epic film "Chariots of Fire" and the Bronze medal sits proudly in the Royal College of Ophthalmologist's Museum, London. The film itself was a huge commercial success and garnered four Academy Awards.[5] Stallard was portrayed in the film by British actor Daniel Gerroll.[5]



Figure 2: Stallard with Dougla Lowe in 1924 olympics. Source: The Olympian Ophthalmologist. Biographical Film by Hugh Williams (https://www.rcophth.ac.uk/about/rcophth/museum)

EARLY OPHTHALMIC CAREER

He got his Medical Degree in 1926 and still continued to run for Britain till 1928 when he was forced to retire due to recurrent stress fractures of both feet. Maybe it was nature's way of telling him that his hands were more blessed than his feet and he had to move on. Stallard was good with his hands and was ambidextrous. This along with his love for surgery probably attracted him to ophthalmic surgery. In the eye department at Barts, he came under the influence of Foster Moore who was conducting research in the conservative management of retinoblastoma by inserting radon seeds at the base of the tumor. By 1929, he was a fellow of the Royal College of Surgeons and was appointed in the Moorfields Eye Hospital as a pathologist and museum curator. He was just 27 years old then. During his work, there he happened to see a lot of retinoblastoma and became interested in improving the management of ocular malignancies. He did extensive research in retinoblastoma and other intraocular malignancies building on his experience with Foster Moore and established the principles of brachytherapy for these tumors. He first used Radium 226 as radioactive applicators and later the Cobalt 60 plaque which he placed on the surface of the eyeball overlying the tumor and could give measured monitored radiotherapy to the tumor.[4,6] He managed to salvage many eyes through these methods and succeeded in popularizing the use of cobalt 60 episcleral plaques for the treatment of choroidal melanomas.

He had his hands full at this time as along with considerable contributions to his chosen subspecialty – the treatment of ocular malignancies, he also filled the positions of Assistant Editor of the BJO and Secretary of the Ophthalmic Society of the UK (OSUK). In addition to the consultancy in Moorfields and St Bartholomew, he was also in the Staff of Queen Alexandra Hospital for Children, The Radium Institute, and Mount Vernon Hospital. But after being accused of not spending enough time in the clinics by Moorfield colleagues, he resigned from there in 1938.


BRITON'S PLUCK
IN OLYMPIC RACE
Stallard Runs with Damaged Foot in 1,500 Metres
FINAL COLLAPSE IN AGONY
Unconscious for an Hour After Finishing Third
From Our Special Correspondent

Figure 3: Stallard lying unconscious besides the track after finishing and a paper clipping of the following day. Source: The Olympian Ophthalmologist. Biographical Film by Hugh Williams (https://www.rcophth.ac.uk/about/rcophth/museum)

THE WAR AND THE BOOK

It was the Second World War which helped Stallard reach the pinnacle of his surgical proficiency and paved the way for the ophthalmic world getting Stallard's master piece work. Stallard held a territorial army commission from 1929 onward. So when the war began in 1939, he rejoined full time in the Royal Armed Military Corps. In 1941, he was posted to Cairo to run a 68-bed ophthalmic unit. He had only 4 nurses, 2 orderlies, and 1 trainee ophthalmologist to assist him. He worked there till Rommel's defeat in 1943.[2,4] During this time, he performed over 600 major surgeries which included war wounds of the eye, eyelids, and orbit and also civilian surgeries such as squint, retinal detachment, glaucoma, and others. He perfected a technique of removing intraocular shrapnel using the surgical giant magnet. He recorded in detail about 100 such cases and published a first of its kind paper on that. He even did six successful appendicectomies which was not surprising as he had qualified as a general surgeon initially.[4]

It was this extensive surgical experience in Cairo that stimulated him to begin his work on his masterpiece book "Eye Surgery" in 1942. Cairo was the place where the Olympian ophthalmologist performed his last athletic world record event. He became the fastest man to climb up and down the "Great Pyramid of Giza". He did that in 13 min and 23 s and the record is probably going to stay as climbing the pyramid is now forbidden.[4] His passion was surgery and research and he hated administrative work. Due to this reason, he declined promotion above the rank of major and this helped him to focus on his work and passion. He then commanded the British Army Base Ophthalmic Unit in Normandy where he had to work in extreme and exacting conditions. No wonder when in 1944, he was transferred to a hospital in Brussels, he wrote "it was odd to tread on a firm floor and have a bath again."[4]

After the war, he rejoined Moorfields and St Bartholomews. It was at this time in 1946 that he published his life's work – the first edition of Stallard's Eye Surgery and it became an internationally accepted reference book on that subject. The next five editions which came out in the span of the next 25 years were also edited by Stallard himself. His artistic talents were in full bloom in the book. The over 600 illustrations that he drew in the book in pen and ink were perfect in every detail. His major field of interest during this time was the conservative management with radiotherapy of intraocular malignancies, especially retinoblastoma and choroidal melanoma and occuloplastic surgery. His exquisite surgical technique along with his patient and dedicated teaching skills attracted students and observers from all parts of the world. His athletic stamina was in display in the operation theater, also where marathon sessions were the norm than the exception.[5] He continued his pioneering work in radiation therapy of malignant eye diseases and perfected the use of brachytherapy for retinoblastomas by stitching radioactive cobalt plaques onto the sclera overlying tumors.

Stallard's life partner Gwynneth Page whom he had married in 1932 was his work partner also. She acted as Stallard's secretary in the smooth running of his practice.

The Stallards travelled widely. His lectures and demonstrations took them to North America, India, Africa, and repeatedly across Western Europe.[2]

AWARDS AND ACCOLADES

For his war time services, he was awarded the Member of the Order of the British Empire in 1942 and was mentioned in dispatches in 1943. He received The Order of the Southern Cross from Brazil for his free services to the underprivileged Brazilian children. He was invited for many prestigious eponymous lectures such as the middle more and the Mckenzie lecture. The prestigious Doyne Memorial Lecture which he gave in 1962 on the conservative management of retinoblastoma was acclaimed world over. He also received a Honorary Doctor of Laws from the University at St Andrews.

A BRAVE ATHLETE TILL THE END

Henry Stallard was an athlete and fitness freak all his life and tried to continue in the same vein as long as he could. Till his retirement from the National Health Service at 65 years, he used a bicycle to travel from his house to his workplace (Moorfields



Figure 4: Stallard arriving for work in his sixties. Source: The Olympian Ophthalmologist. Biographical Film by Hugh Williams (https://www.rcophth.ac.uk/about/rcophth/museum)

or St Bartholomew) and always arrived earlier than his colleagues who struggled with their motor cars in the London traffic [Figure 4]. After parking his bike, he would run up four flights of stairs to his office with his house surgeon and registrar panting after him. But then, it was sad that the same fate that broke his lower limb bones and denied him an Olympic gold medal in 1926, struck once again in 1972, this time threatening not only his limbs but also his life. He developed Paget's disease of the pelvic bone and that too complicated with estrogenic sarcoma. But did he also force fate's hand by routinely carrying unshielded radioactive plaques in his hip pocket as he went from hospital to hospital treating intraocular malignancies, before his retirement. The sarcoma was most likely radiation induced.[5] He was at that time elected as the President of the OSUK and 2 days after his brave presidential address in April 1973 (he had received a blood transfusion that very morning) resigned due to deteriorating health. He struggled on in his private practice for 6 more months braving the pain, inconveniences of multiple blood transfusions, and side effects of radiation therapy and finally wrote to his patients that he will have to retire in October. But he did not have to as he died rather suddenly at his home in 21 October 1973. He was 72 years' old. The man who saved the lives and eyes of millions of children worldwide thanks to his pioneering work in retinoblastoma management however did not have any of his own.

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IMPACT OF COVID-19 PANDEMIC ON UVEITIS PATIENTS RECEIVING IMMUNOMODULATORY AND BIOLOGICAL THERAPIES (COPE STUDY)

Aniruddha Kishandutt Agarwal, Sridharan Sudharshan, Padmamalini Mahendradas, Kalpana Babu, Pratik Shenoy, Mohit Dogra, Reema Bansal, Manisha Agarwal, Jyotirmay Biswas, S. Balamurugan, Rupesh Agrawal, Vishali Gupta

High dose of corticosteroids and immunomodulatory therapies (IMTs) are considered to be the mainstay of management in uveitis. Patients on these drugs are prone to COVID-19 infection and may be subjected to severe forms of disease. It was in March 2020, during the early stages of the pandemic, uveitis specialists became concerned about the use of high-dose therapies in their patients. It is in this backdrop, a study was undertaken to assess the impact of this pandemic on uveitis management, which forms the basis of this paper.

This study was done as prospective case series in which 284 eyes from 176 patients were included. Noninfectious uveitis (NIU) patients who received corticosteroids, IMTs, and biologicals in the pre-COVID period and who were subjected to follow-up during the period between March 1, and June 25, 2020, were considered for this study. Clinical details, disease activity, time since the last activity, and treatment history of each subject were recorded with the intention of identifying relapse of disease if any, and evaluation was done at regular intervals. Data were collected online, and statistical tools such as descriptive analysis and Mann–Whitney U-test were used.

Out of 176 patients, 108 have bilateral disease. Ninety patients had active NIU and remaining were quiescent on maintenance therapy. Among eyes with active NIU, 12.2% were given intravenous methylprednisolone (IVMP) for severe vision-threatening uveitis. However, in 7.77%, the uveitis experts preferred to not treat with IVMP despite an indication for the same. Among active NIU patients who were started on oral corticosteroids, rapid tapering was done in 57.4%. No alterations were made for those on maintenance therapy (≤10 mg/kg/day dose). 161 (91.5%) patients were receiving systemic IMT, and 25 patients (14.2%) were given biological therapies. IMT was altered in 29/161 (18.0%) subjects, but no alterations were made with biological agents.

Among eyes with inactive NIU (n = 163 eyes), relapse was noted in 53 eyes (32.5%, 29 subjects), and 24 subjects had relapse in both eyes. Of the nine subjects who stopped medications, five developed active uveitis. All these subjects were treated with a bridge course of oral corticosteroids and frequent topical corticosteroids/intravitreal injections. None of the subjects developed symptoms related to COVID-19 during the study.

Based on the observations, it was found that, in the case of patients with stable on-going therapies for NIU, sudden reduction in dosages can result in increase in recurrences. Hence, the implication of the study is that a major deviation from the current treatment practice will lead to a not so desirable outcome in case of uveitis patients. The uniqueness of the study lies in the time period during which it was conducted.

The study has certain limitations. It does not mention how many subjects were eligible for inclusion and how many potentially eligible subjects came to the hospital for follow-up. Had these details been included it would have been possible to get an idea about the number of patients having relapse or worsened symptomatology but unable to access hospital care. This is an observational study and cannot determine the therapeutic value or clinical utility of therapies. The number of COVID patients was very low during the study period. Hence, the study has constraints in authentically proving the impact of this pandemic on uveitis treatment.

The study concluded that during the COVID-19 pandemic, uveitis specialists may tend to reduce the ongoing systemic IMT or prefer less aggressive treatment strategies for NIU, which put these subjects at high risk of uveitis relapse.

DIFFERENTIAL EFFECTS ON OCULAR BIOMETRICS BY 0.05%, 0.025%, AND 0.01% ATROPINE: LOW-CONCENTRATION ATROPINE FOR MYOPIA PROGRESSION STUDY

Fen Fen Li, Ka Wai Kam, Yuzhou Zhang, Shu Min Tang, Alvin L. Young, Li Jia Chen, Clement C. Tham, Chi Pui Pang, Jason C. Yam

High myopia is associated with sight-threatening complications such as macular hemorrhage, retinal detachment, cataract, and glaucoma. These complications have an adverse effect on the quality of life of affected persons, and moreover, the economic burden in managing them is relatively high. It is a universally accepted fact that atropine eye drops in low concentrations can delay the

myopic progression. The present study was done taking into consideration of this fact.

The study aims at determining which all factors affecting myopic progression can be arrested by providing atropine in various concentrations. Hence, the purpose was to evaluate changes in ocular biometrics in groups receiving 0.05%, 0.025%, and 0.01% atropine compared with placebo over 1 year based on the Low-Concentration Atropine for Myopia Progression (LAMP) study. This was a double-blinded, randomized, placebo-controlled trial.

The study population included 383 children who had completed 1st year of LAMP study in the age group of 4–12 years, who had been given different concentrations of atropine or placebo once daily in both eyes. Of the total, 102 were in the 0.05% atropine group, 91 in the 0.025% atropine group, 97 children in the 0.01% atropine group, and 93 children in the placebo group.

IOL Master was used to measure cycloplegic spherical equivalent (SE), axial length (AL), corneal curvature (K), and anterior-chamber depth (ACD). Corneal astigmatism and lens power were calculated. The ocular biometric parameter changes were compared among groups. Contributions to SE progression from ocular parameters were determined and compared among groups.

Over 1 year, the changes in AL were 0.20 ± 0.25 mm, 0.29 ± 0.20 mm, 0.36 ± 0.29 mm, and 0.41 ± 0.22 mm in the 0.05% atropine, 0.025% atropine, 0.01% atropine, and placebo groups, respectively ($P < 0.001$), with a concentration-dependent response. This study demonstrated that largest reduction in AL was found in subjects who were given 0.05% atropine. Changes in ACD remained similar across all concentrations. AL elongation contributed most of the SE progression. Corneal power remained stable, and its changes were similar across all atropine concentration. Lens power decreased over time in each concentration, but its changes also were similar across all concentrations.

The major strength of the study is its methodology. Possible biases were minimized by using generalized estimating equations. There is direct comparison between different atropine concentrations with placebo in the study. To avoid the effects of accommodation, measurements were done after complete cycloplegia.

However, the study is not free from limitations. The current study reported only the 1st-year period of atropine treatment compared with the placebo. Further, lens power was not measured directly. The future scope is that further studies can be conducted to evaluate the long-term ocular biometric changes after stoppage of treatment.

From the findings of this study, it can be concluded that antimyopic effect of low-concentration atropine was achieved mainly by retardation of axial elongation. Low concentrations of atropine have no clinical effect on corneal or lens power.

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Basics of eye donation

ABSTRACT

This writeup deals with the basics of Eye Donation, from who can and cannot donate, how to counsel patients, how to pledge one's eyes, the responsibilities of a donor's family in the donation process. It also touches upon removal of the donor corneal tissue, processing and preservation of donor cornea at the Eye Bank, and the impact of COVID-19 on the eye donation scenario.

Keywords: Corneal storage media, COVID and eye donation, eye donation, pledge eyes

INTRODUCTION

The concept of replacing a compromised cornea with a clear one has been around for thousands of years. As an experimental procedure, it was performed in animals long before an attempt was made on human eyes. The first reported xenograft corneal transplantation goes back to the year 1838, which was, unsurprisingly, unsuccessful.

The first corneal transplant using an allograft was reported as far back as the year 1905, by Dr. Eduard Zirm, an Ophthalmologist from Austria, on a patient who had sustained severe bilateral alkali burns 15 months earlier. Interestingly, the donor corneas came from a living donor, an 11-year-old male child who had suffered a scleral penetrating injury.[1] The eye was enucleated, and two donor corneal buttons of 5 mm were fashioned. Zirm attempted simultaneous keratoplasty in both the eyes and the intra-operative period was uneventful.

The vision was gradually lost in the right eye due to complications from the surgery (widely believed to be because of wound dehiscence); while the graft in the left eye remained clear, and the patient regained useful vision in that eye.[2] This was a huge milestone in the history of medicine, considering the limitations of knowledge at the time and paucity of surgical equipment capable of such an intricate procedure. However, this procedure almost single-handedly proved the efficiency of using a human donor over a xenograft.

The first corneal transplant in India was performed by Dr. RES Muthiah in 1948, and he is also credited with establishing the first Eye Bank in India. Today, the Eye Bank Association of India is the center for eye donation and eye banking in the country and the main force behind the creation of public awareness regarding the need for donors.

The recent advances in surgical equipment, microscopic precision cutting technology with femtosecond lasers, deeper understanding of corneal microstructural anatomy and immune mechanisms have all led to the possibility of up to four recipients benefiting from a single donor.

DONOR CRITERIA

- Anyone between the age of two (this is sometimes even

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reduced to 1 year of age) and seventy can be donors, though donation beyond the age of seventy is not discouraged. The upper limit only exists as a benchmark where corneal decompensation might have started due to the significant fall in the number of endothelial cells by the seventh decade. Corneas from donors less than a year of age are mostly used for research purposes

- Corneal donation from a living donor is seldom encouraged, as it is widely accepted that having good vision in both eyes is a basic human right and necessity. There are, however, very rare instances in which living donors can be considered. In case of a penetrating injury of the eye that does not involve the cornea; the eye undergoing enucleation can be used for corneal donation. In these types of cases, the entire eyeball cannot be preserved, and hence, an *in-situ* excision of the donor corneal button is done, and the sclero-corneal button alone is preserved
- In some instances of unilateral retinal pathologies, where there is no perception of light in one eye, and the patient has corneal blindness in the other, an autograft procedure can be considered if it ultimately bestows useful vision to the patient.

CONTRAINDICATIONS FOR EYE DONATION

- People who have undergone LASIK cannot be donors since the cornea has already been surgically manipulated, and the shape of the corneal button obtained from such eyes might not be ideal. The question of survival of the delicate corneal tissue after undergoing two surgical procedures has also raised concerns regarding endothelial cell viability
- If death is due to unknown causes, or the person suffered a central nervous system disease of unknown etiology, the person cannot be a donor
- People at high risk for human immunodeficiency virus (HIV) such as intravenous drug use, people with active leukemia, disseminated lymphoma, active septicemia, ocular neoplasms, or other neoplasms that cause ocular seeding cannot be donors
- In the case of pediatric donors, an eye that is < 1 year of age is generally not used for transplantation, and the donated eye is used instead for research purposes
- An eye with active inflammatory disease, any stage of retinoblastoma or malignant melanoma is not acceptable for donation
- Other than these specific restrictions, the same rules that apply to any other organ donation apply here. People with communicable diseases cannot be donors. Rabies, subacute sclerosing panencephalitis (SSPE), Creutzfeldt-Jacob disease, and other suspected prion diseases are contraindications.

The Food and Drug Administration testing requires HIV, Hepatitis B, Hepatitis C, syphilis to be ruled out. At the time of enucleation, a sample of blood is taken from the donor for this reason.

RESPONSIBILITIES OF A DONOR

Anyone above the legal age of 18 can pledge their eyes. This can be done online, on the Eye Bank Association of India website; or, if you wish to donate other organs as well, on the website of the Organ Receiving and Giving Awareness Network. It can also be done in the Department of Motor Vehicles while applying for or renewal of a driving license. Donor information is usually mentioned on the license itself.

In addition to this, it is important for a person to keep their family members informed regarding their pledge.

RESPONSIBILITIES OF THE FAMILY MEMBERS OF A DONOR

In case a person who has pledged their eyes passes away, the family needs to intimate the nearest Eye Bank as soon as possible. The Organ Receiving and Giving Awareness Network, on their website (www.organindia.org) provides the location and contact information of the nearest Eye Bank. If a person, in life, has not pledged their eyes; the next of kin has the right to donate their eyes. The cornea should be harvested within six to eight hours of death; the earlier, the better. This is because the endothelium of the cornea is in apposition to the necrotic and metabolic substances in the stagnant aqueous humor.

The eyes should be kept closed, and a moist cloth is to be applied on the lids. It is advised that the family keep the fans switched off in the room to prevent drying of the ocular surface. If possible, they can keep humidifiers and air conditioners on. The head end should be elevated to prevent edema of the cornea, which might lead to a loss of transparency; and decreases congestion in ocular blood vessels, which in turn reduces blood loss during enucleation.

The Eye Bank team arrives at the residence, and the procedure is carried out at home.

HARVESTING THE CORNEAL GRAFT

The consent of the next of kin is necessary for the procedure to be carried out. The procedure is either enucleation or an *in-situ* removal of sclerocorneal button. What is preferred

is that the whole globe is removed, but once taken to the Eye Bank, only the corneoscleral button is excised and then preserved. As mentioned before, preserving the whole globe would mean that the endothelium remains in contact with aqueous humor that rapidly fills with metabolic by-products that adversely affect endothelial cell health. Another point in favor of doing a whole globe removal is that enucleation takes less time, and time need not be wasted doing an *in-situ* corneoscleral button incision in a cornea that is later deemed unacceptable in the preliminary screening itself.

Once the procedure is complete, a gauze ball, ocular prosthesis, or keratoprosthesis is placed, and the lids are sewn shut. A 10 ml sample of blood is also withdrawn to run serological and other tests. The enucleated eyeball is placed, cornea up, in a moist chamber. In the case of *in-situ* excision of a corneoscleral button, they are stored endothelial cell side up, in either McCarey Kaufman medium, Cornisol, or Optisol GS.

DONOR CORNEA EVALUATION

Once they are brought back to the Eye Bank, they undergo a donor cornea evaluation process. This starts with the blood sample, and once this is cleared, the cornea itself undergoes evaluation under a microscope, and specular microscopy is done in most cases. This process standardizes and streamlines the quality of donor corneas.

During this process, the cornea may also be precut to be used for the next procedure, either a lamellar keratoplasty or a full-thickness keratoplasty. Doing this in the Eye Bank itself decreases valuable surgical time while the cornea is being transplanted.

STORAGE OF DONOR CORNEA

The various storage techniques are classified based on the duration of storage[3], as listed in Table 1.

Before the cornea is used for transplantation, make sure that the seal is intact, check the expiry date and look for signs of contamination (pH change, turbidity).

EYE DONATION COUNSELLING AND AWARENESS

Counseling for eye donation yields better results when done in the ward, rather than in the mortuary. The two sources of donated corneas are voluntary pledging by the well-informed public, or the creation of awareness among patients and their families by the Hospital Cornea Retrieval Programme (HCRP), wherein potential donors are identified and recruited by a combination of motivation and grief counseling. The team can include hospital staff, doctors, and grief counselors, who are usually stationed near critical care complexes of the hospital (intensive care unit, critical care unit). Trained eye donation counselors are available round the clock, and this way, the option of donating one's eyes reaches even those without prior knowledge of eye donation.

The formation of an HCRP team can help ease the donation process since a detailed history of the patient's medical profile is already known, and as it is done in a hospital setup, there is a shorter interval time between death and corneal harvesting. The individuals in the team should have a sound knowledge about eye donation, should be able to dispel any myths about eye donation, and should be able to motivate and counsel the family through the entire process while giving due respect to the deceased.

It always helps if the following points are touched upon during the counseling or awareness programs. No religion is against eye donation, though this is the single largest argument against eye donation people have even today. Donating your eyes does not cause disfiguration of the face or body in any way. Two donated corneas can help up to four people. It must be made clear that eyes, once donated, or any other organ for that matter, cannot be bought or sold. It is a humanitarian act that no one can put a price on. The eye, once donated, cannot be tracked. There is no way of knowing who the eye goes to or comes from, and everything is kept anonymous (except in the few rare cases mentioned above).

IMPACT OF COVID-19 ON EYE DONATION

The number of elective surgeries has drastically dropped since the pandemic rolled in, but keratoplasty is not always an elective procedure. With reports that the COVID-19 virus has been isolated from tear samples, it remains prudent that corneal harvesting be kept to a minimum as of now, considering that the procedure might endanger the health of the collection team and the fact that it is too early to comment on COVID transmission through transplanted organs. Usage of alternative methods to preserve the globe in case of emergencies until such time as a vision-restoring procedure can be performed has been proposed.[4]

On May 8, the Ministry of Health and Family Welfare had declared that Eye Banking activities could be done only in non-COVID hospitals. As of August 19, 2020, the Ministry suspended voluntary eye donation and strictly advised against eyeball retrieval from homes. However, they have stated that HCRP can be continued in hospitals for corneal retrieval from non-COVID cadavers for therapeutic purposes.

Table 1: Corneal Storage Media

	Duration	Temperature	Technique/media	Additional information
Short-term	Not more than 24 h	4°C	Moist chamber	The simplest method of storage is the moist chamber, which is a sterile jar that contains normal saline; and maintained at 4°C
	Upto 4 days		McCarey Kaufman medium	It contains dextran to maintain the osmotic gradient across the cornea, gentamycin for greater gram-negative cover, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) as buffer and phenol red as an indicator
Intermediate storage	14-16 days	4°C	Dexol	Dexol contains dextran in a base of minimal essential medium, and this overcame the issue of corneal swelling due to chondroitin sulphate
			Eusol-C	Similar to Dexol, but contains glucose in addition to dextran
			Optisol	Optisol uses a combination of minimal essential medium and tissue culture medium as a base, and a slightly higher concentration of chondroitin suphate than Dexol. This has been shown to preserve endothelial cell morphology and corneal contour better than its counterparts
			Optisol GS	Optisol GS contains two antibiotics - gentamycin and streptomycin, in Optisol medium, for broad spectrum coverage
			Procell	Procell contains human insulin and human epidermal growth factor, thought to improve endothelial survival after a penetrating keratoplasty
Long-term storage	28 days	31°C	Eurosol	This is a long-term storage media that does not contain components of bovine origin, such as calf-serum
	120 days	37°C	European Organ Culture	The advantage of organ culture is that refrigeration is not required but necessitates high technical knowledge on the part of the microbiologist. It contains penicillin, gentamicin, and amphotericin. Depending on the media used, it might have to be replaced after two weeks
Very long-term storage	Upto 5 years	4°C	Anhydrous glycerol	Corneas can be preserved in 100% glycerine, but this procedure essentially damages the endothelium and renders it non-functional. These corneas are used for lamellar procedures that do not involve the donor endothelium being transplanted
	Unlimited storage	−80°C	Cryopreservation	The cornea can be stored for an unlimited time in liquid nitrogen. Dimethyl sulfoxide in the media prevents intracellular damage due to ice crystal formation. Cryopreserved corneas cannot be used for transplantations but are used extensively in research avenues

On September 1, the EBAI published its revised guidelines for cornea retrieval and eye banking activities during the COVID era.[5] Numerous precautions have been advised during the retrieval and transport of donor corneas.

All staff and technicians involved in the counseling and retrieval process should be equipped with a full personal protective equipment kit. Enucleation is not advised, and only the excision of the corneoscleral button is advocated. Before the procedure, double contact with povidone-iodine is advised. All collected tissues are to be quarantined for 48 hours prior to usage for transplantation.

Exclusion criteria for eye donation during the COVID-19 era have been enumerated.

- If the person has tested positive for COVID-19
- If the individual has reported or experienced any symptom known to be associated with COVID-19 (acute respiratory illness, fever, cough, shortness of breath, diarrhea)
- Individuals who have been exposed to a confirmed or suspected case of COVID-19 within the last 14 days
- Persons who have visited the containment zone within 14 days of death
- If the deceased had evidence of conjunctivitis, acute respiratory distress syndrome, pneumonia, or computed tomography scan showing ground glass opacities (regardless of whether another organism has been identified).

Collection of a nasal swab of the deceased donor for COVID-19 reverse transcription-polymerase chain reaction can be done, though this is solely under the discretion of the Medical Director of the institution. Eye banks throughout the country have been advised to follow their respective local state government guidelines regarding their extent of activities.

PG PEARLS ON EYE DONATION

Bioengineered corneas are corneal equivalents made of cellular scaffolds from recombinant human collagen and synthetic phosphorylcholine polymer. They have been proposed for usage in anterior lamellar keratoplasty procedures rather than full-thickness grafts. However, the consensus remains that a cornea from a donor remains superior to anything made under laboratory conditions

- Isolated endothelial cell injections have been done, and recent advances have shown their efficacy in cases of corneal edema

- Most of the rejection reactions are due to the presence of donor corneal endothelium, and this is the reason anterior lamellar keratoplasty has a much lower failure rate than a graft that involves donor endothelium
- In the case of congenital corneal opacities, the child should be operated on as soon as possible to prevent the development of strabismus or amblyopia. It is always better to use age-matched corneas, especially in young children. In adults, a slightly younger donor than the recipient is preferred, but this is not a strict criterion
- There are a few rare instances where eyes can be donated before death, as enumerated above.

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Conflicts of interest

There are no conflicts of interest.

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Author's reply to comments on "comparison of the scleral tunnel constructed with crescent versus razor blade using the anterior segment optical coherence tomography"

Dear Sir,

We appreciate the interest of authors Kaur and Gurnani, in our article entitled "Comparison of the scleral tunnel constructed with crescent versus razor blade using the anterior segment optical coherence tomography" published in the September–December issue of your esteemed journal,[1] and thank them for their gracious comments.[2]

We wish to reply to the interesting queries raised:

1. The baseline incision length of the tunnel constructed was 5.5–6 mm on an average in all cases. The tunnel in case mentioned in abstract as having premature entry was also similar. Further, considering the fact that it was performed by a single surgeon and that all the cases were uncomplicated the details missed mention in the results section
2. We at our institute here in the community section use the razor blade routinely for all our cases. We agree that a triplanar section is difficult with straight instrument like razor blade, but with temporal sections where eye can be moved to allow blade to reach the end of tunnel and ensure getting a dimple before entry, self-sealing section [almost a triplanar section; Figure 1] is obtainable We agree that complications will be higher in inexperienced hands but in experienced hands, as seen in our study, it is a safe alternative. In beginning phases, just few steps of getting the incision and getting plane of section right is taught with blade (confirmed with crescent every time) and eventually moving up to performing the entire section with the razor blade. Moreover, this is only after learning the tunnel construction with crescent blade.
3. With respect to the standardization of time measurement, a stop watch was used by the assisting author in observation, to record the exact time of start and completion of the tunnel construction, in synchrony with direct observation of the procedure
4. The tunnel depth difference mentioned was according to anterior segment optical coherence tomography (62 μ difference in the mean depth). This difference in depth did not warrant suturing or intraoperative complications in our study. In cases that required suturing, which was observed in 2 cases, 1 each in the blade and the crescent group, the indication was a deeper plane of construction in both. The width of the tunnel was same in both the groups though that was not a part of our study
5. Finally, the depth of the tunnel constructed in case of the patient with Descemet membrane detachment (DMD), the depth at external entry was 507 ∝, while that at the internal plane was noted to be 523 ∝. The DMD in this case was detected on table and hence managed immediately, thus improving the final outcome.

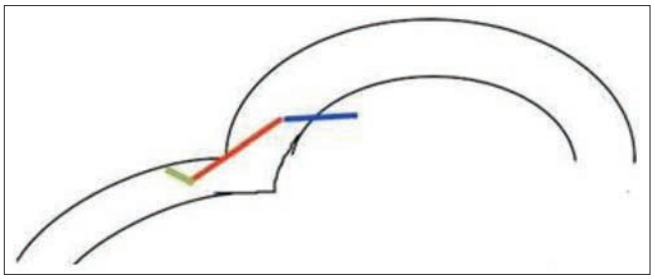


Figure 1: self sealing, triplanar section

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The green glaucoma cricket championship: An innovative glaucoma titled based cricket match initiative for screening and promoting awareness on glaucoma disease process and compliance

ABSTRACT

World glaucoma week is celebrated annually in the 2nd week of March, to raise awareness on glaucoma. In the light of the existing manpower and resource constraints, we propose this novel concept of glaucoma awareness, through the green glaucoma cricket championship. The overarching goal of this cricket championship was to screen the general public attending the event with noncontact tonometry, confocal fundus scanner and portable virtual reality perimetry; and refer suspicious patients to the base hospital. Every single protocol of this cricket match was specifically designed with a glaucomatous nomenclature, so that the public gathering, can be educated with those terminologies at various phases of the match. Two hundred and twenty people visited during the 3 h awareness cricket match. A total of 154 people above the age of 40 years were screened for glaucoma, of which 15 (9.7%) were found to be glaucoma suspects, and were referred to the base hospital. Ten out of 15 (66.6%) glaucoma suspects presented to the hospital during the glaucoma awareness week 2020, of which 4 (40%) were confirmed to have glaucoma. This manuscript highlights the promotion of awareness and knowledge toward glaucoma, to the general public through cricket, because in India cricket is like religion and Indian's love for the sport is unparalleled.

Keywords: Cricket, glaucoma awareness, glaucoma titled-based cricket match, green lapel ribbon

World glaucoma week is celebrated annually in the 2nd week of March, as a global joint initiative between the World Glaucoma Association and the World Glaucoma Patient Committee to raise awareness on glaucoma. Raising public awareness and spreading knowledge about glaucoma are the key for preventing irreversible blindness as individuals at risk may need to be more aware and seek timely assessment to diagnose this condition early.[1]

On the basis of the available Indian data, it is estimated that there are approximately 11.2 million aged 40 years and older with glaucoma; with primary open-angle glaucoma patients comprising approximately 6.48 million, primary angle-closure glaucoma comprising approximately 2.54 million and any form of primary angle-closure disease comprising 27.6 million.[2] Most of those with the disease are undetected and there exist major challenges in detecting and treating them. In the light of the existing workforce and resource constraints, we propose this novel concept of glaucoma disease and compliance awareness among people, through the green glaucoma cricket championship between two pre-decided teams of eleven members named as open-angle gladiators (OAG) and angle-closure sixers (ACS).

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The green glaucoma cricket championship was conducted on March 8 2020 with doctors and paramedical staffs of XXX representing the OAG team and ACS team. The teams were named with glaucoma terminologies to instruct the public gathering about the two different variants of glaucoma. The name and color of the match were inspired from the green lapel ribbon logo [Figure 1] used for glaucoma awareness. Teams were provided with two contrasting green color jerseys, i.e., OAG team jersey was predominantly white in color with green lettered names on the back and ACS team jersey was predominantly green in color with white lettered names on the back, respectively [Figure 2].

The overarching goal of this match was for the general public attending the event, to know about the disease called "glaucoma" and screen them with noncontact tonometry, confocal fundus scanner (Eidon, CenterVue, Italy), and portable virtual reality perimetry (Elisar Vision Technology). Informed consent was obtained from each participant willing to undergo screening. If they were diagnosed with either high intraocular pressures or suspicious cups or specific glaucomatous visual field (VF) defects, they were referred to the base hospital for further detailed evaluation free of cost, if they reported to the hospital within the world glaucoma week (8–14 March 2020).

Every single protocol of this cricket match was specifically designed with a glaucomatous nomenclature so that the public gathering can be educated at various phases of the cricket match. The match started with the "Gonioscopic Toss" [Figure 3]. The nomenclature in naming the toss with "gonioscopic" prefix was; the captain calling for it either called open angles (i.e. heads) or close angles (i.e., tails) instead of the routine heads or tails.

All awards were named based on the diagnostic and treatment components [Figure 4] of glaucoma. The championship award for the team winning the match was named "Green Glaucoma Cricket Championship." The player of the match was named "Ocular Hypertensive Man of the Match" with the leading run-scorer being awarded the "Applanative Tonometric Batsman," most economical and wicket taking bowler being named "Compliant Economic Bowler," and most electrifying fielder being named "Gun Visual Fielder."

As it is well known, intraocular pressure (IOP) is the only modifiable risk factor, we have named the player of the match as ocular hypertensive man of the match, as he is the predominant game changer, just like the modifiable IOP for glaucoma therapy. Applanation tonometry terminology was given as suffix to the best batsman who guided his team with the bat, just like how the applanation tonometer guides in measuring IOP and diagnosing glaucoma patients. Compliance terminology was given as suffix to the best

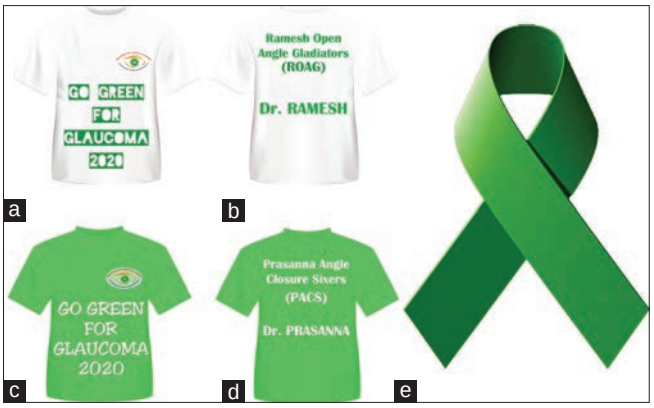


Figure 1: The team jerseys named after the two different variants of glaucoma manifestations in view of glaucoma awareness week are shown here. (a and b) The front and back aspect of the jersey for team open angle gladiators are shown. (c and d) The front and back aspect of the jersey for the team angle closure sixers are shown. (e) The green ribbon lapel signifying glaucoma awareness week



Figure 2: (a and b) The green cricket jersey unveiling done for the team open angle gladiators and team angle closure sixers respectively



Figure 3: (a) The inauguration of the "Green Cricket Championship". (b) The gonioscopic-toss performed before commencement of the game. (c) The cricket kit utilized for the game along with the trophies



Figure 4: The various awards named in-order to depict the important aspects in glaucoma awareness are shown here. The various awards are as follows: Green test championship, ocular hypertensive man of the match, applanative tonometric batsman, compliant economic bowler and gun visual fielder

bowler because economical bowling by preventing runs and taking wickets with the ball, just like good compliance toward antiglaucoma medication is very important to have adequate control over the reduction of runs (i.e., reduction of IOP). VFs terminology was given to the best fielder of the match, who just like the VF machine, scans the field of the cricket ground saving runs (i.e. diagnosing defects).

Not only did we emphasize on glaucoma diagnoses but also stressed the role of compliance. As the famous saying goes, "Batsmen win you matches, but bowlers win you tournaments." Similarly, our motto of this Green Glaucoma Cricket Championship between the OAG and Closed Angle Sixers was "Glaucoma diagnosis win you matches, but compliance toward therapy, follow-up and re-treatment if necessary win you the tournament."

Different strategies of glaucoma awareness have been reported in literature but according to our knowledge, this unique innovative awareness module has never been reported before. As people in India absolutely love the cherished sport of cricket, from kids playing it in the streets to the oldies having the fun of it at their home, cricket has grown to be a widely popular sporting event in India, especially after the inception of the Indian Premier League. Hence, we have initiated glaucoma awareness through cricket [Figure 5] to cater to a wider audience.

Two hundred and twenty people visited during the 3 h awareness match. A total of 154 people above the age of 40 years were screened for glaucoma, of which 15 (9.7%) were found to be glaucoma suspects and were referred to the base hospital. Ten out of 15 (66.6%) glaucoma suspects presented to the hospital during the glaucoma awareness week 2020, of which 4 (40%) were confirmed to have glaucoma.



Figure 5: (a and b) Bowling done by team angle closure sixers and batting done by team open angle gladiators are shown here. (c and d) Teams discussing gaming strategies during fall of a wicket are shown here

Raising public awareness and knowledge of glaucoma is the key for addressing the overwhelming consequences of this disease.[3] Hence, this manuscript aimed to promote awareness and knowledge towards glaucoma and associated factors through cricket, because in India, cricket is like religion and Indian's love for the sport is unparalleled.

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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