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Central Picture:

Central Areolar Choroidal Dystrophy
It is characterised by outer retinal atrophy with loss of choroidal tissue in the macular area which is bilateral and symmetrical. Photo courtesy: DR. Priya Chandrasekharan.

Bottom picture
This is a picture of a Retinal Ganglion Cell (an RGC), where the nucleus stain DAPI is in blue, cell marker for RGC's beta III tubulin is in green and the red puncta are PSD-95. Beta III tubulin in green is a pan-RGC marker, therefore it is not possible to distinguish which neuronal process is the axon in this neuron, perhaps it wasn't fully differentiated. The red dots are synapses. Photo courtesy: Dr. Rachel Chong.

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Editorial

Awareness about Eye Health in Kerala

As ophthalmologists, we are a witness to a paradox on almost every day of our clinical practice, which perhaps is unique to our state, Kerala. We find patients visiting private clinics armed to the teeth with all the information about a particular disease from Google, asking so many questions that it makes the doctor defensive. On the other hand, we find patients visiting government hospitals without any awareness about their disease. So much so that there are patients who have been diabetic for more than 25 years and yet they have never undergone an ocular examination! They have never been advised for an ocular examination, nor have they found out by themselves that it is essential. Why is it that the most literate state of India has such diametrically opposite levels of awareness about eye diseases?

In a study by Dandona *et al*.[1] in 2001, 69.8% of the respondents were aware of cataract, but only 27% were aware of diabetic retinopathy and 2.3% were aware of glaucomas in the urban population of Hyderabad. In a hospital-based cross-sectional study performed at Kozhikode, 66% were aware that diabetes could affect the eye, yet 51% had an eye check-up only when they had symptoms.[2] In another study by Misra *et al*.,[3] to assess the awareness and health-seeking practices about cataract among the people aged 18–60 years living in slum areas in Delhi, most participants have heard of cataract, but there is low awareness of its symptoms and treatment. Good eye health-seeking practices were observed for cataract in that urban slum population. Most of the studies about awareness are hospital-based studies, and therefore, extrapolating their conclusions to the general population becomes untenable.

Besides the ubiquitous social media forward of health-related messages, which may or may not be fake – the downside of information revolution – most of the people come to know about eye diseases only if a family member or a close relative or a friend is suffering from the disease. The people with a higher level of education and a higher socio-economic status use search platforms such as YouTube and Google to garner information about their health or disease. However, it is the people in the lower socio-economic strata who remain ignorant and fall prey to the morbidity and sometimes the mortality of the event. A common example of this is the assumption by many patients that all cases of painless loss of vision are because of cataract, and so important conditions such as diabetic retinopathy and glaucoma are neglected.

It is high time that we ophthalmologists introspect among ourselves and examine our role in propagating awareness about ocular diseases or ocular manifestations of systemic diseases. Are we doing enough? We celebrate the World Sight Day, The Glaucoma Week, and the Eye Donation fortnight and pat each other's back once we have filed the pictures to our respective ophthalmic societies. A cursory glance into the celebrations would tell us that we are using them more as photo-opportunities for ourselves rather than as meaningful ways of disbursing information to the public. Instead of tokenisms by organizing online felicitations and educational meetings by the ophthalmologists for the ophthalmologists, sincere efforts must be made to percolate the awareness to the masses.

We must involve the nursing students, medical students, and other paramedical staff to speak to the public about the ocular diseases. This connect should be exercised not using complex medical terminologies but in a simple language that the patient and public can understand. This can be in the form of posters, exhibitions, and seminars among the patients in hospitals, rather than conducting online meetings in the off-hours. At the Primary Health Centre level and at the Non-Communicable Diseases Clinics level, we must conduct regular sessions of talks on eye diseases on different days of the week so that different patients benefit. We must have a holistic approach to improving health services in by tackling barriers at different levels, considering local context and geo-spatial features of individual communities.[4]

The social media have demonstrated their power with respect to their reach and educational value. The Kerala Society of Ophthalmic Surgeons is pitching in by conducting interviews with senior ophthalmologists to share their experiences and by disseminating bite-sized clips of those programs. The school-based programs have enabled greater awareness of refractive errors. Camps have spread knowledge about cataracts. We need more of screening camps for diabetic retinopathy. The public should be encouraged to visit an ophthalmologist at least once every 2 years if they are healthy to undergo a fundus examination. The Government must also incentivize it.

Artificial intelligence (AI) is emerging as a major tool in diagnosing eye diseases. Innovative medical exhibitions, installations, or floats in both rural and urban areas can be used to catch the attention of people and make them aware about eye diseases. A smartphone-based, slit lamp-mounted fundus-on-phone (FOP) camera for early detection of glaucoma and diabetic retinopathy uses AI to pick up glaucoma/disc suspects or diabetic retinopathy cases from the fundus images. This will reduce the doctor's workload and patients' unnecessary travel expenditure yet guide them toward the right treatment.[5]

Poor socio-economic status and illiteracy are the key factors for such a poor level of awareness in India. We have just celebrated the 75th Independence Day, and this is a major milestone for India. We must propagate scientific literacy not only among the public but also among the teachers and students. Another important aspect is expansion of advocacy—the most undeveloped component of health promotion which is essential to convince governments to channel increased resources to eye health promotion.[6]

The physicians are the primary contact for most patients with systemic diseases. Case detection is the approach to the problem of eye diseases other than cataract. For case detection, awareness and knowledge among the public are very important so that they come forward for routine eye examination.[7] The Government must also incentivize those physicians and ophthalmologists who spread awareness. The network of hospitals from the level of primary health centers to the tertiary care centers is strong and vibrant in our state. Let us take this opportunity to critically assess our successes and failures and prepare for a promising future.

Smita Narayan

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Prevention of postoperative endophthalmitis – some random thoughts

Postoperative endophthalmitis (PE) is the most dreaded complication in any intraocular procedure. Most PE are exogenous and are preventable by diligent observance of disinfection and sterilization procedures and control of risk factors. Some of the procedures that we follow, like use of perioperative systemic or topical antibiotics, do not have any scientific backing. On the other hand, use of povidone iodine solution has proven benefits.[1] The prospective European Society for Cataract and Refractive Surgery (ESCRS) study advocates the role of intracameral (I/C) cefuroxime in lowering PE. Several surgeons were using Moxifloxacin drops intracamerally for many years. But the landmark study by Haripriya *et al*.[2] in a retrospective analysis of more than 6 lakhs eyes compared the PE rate before and after initiation of intracameral moxifloxacin prophylaxis for both phacoemulsification and sutureless manual small-incision cataract surgery (M-SICS) and in patients with posterior capsular rupture. There was a three-fold reduction in PE in the M-SICS group with I/C Moxifloxacin, whereas it was a six-fold reduction in Phacoemulsification. This study has emphasized the role of intracameral Moxifloxacin in all routine intraocular surgeries. However, endophthalmitis prophylaxis failures with intracameral antibiotics after phacoemulsification have also been reported.[3] Of the 216,141 surgeries in a study in Northern California, endophthalmitis occurred in 0.020% of moxifloxacin-injected eyes and 0.013% of cefuroxime eyes. Of the 34 (0.016%) cases of endophthalmitis in which cefuroxime 1 mg was injected into 13 eyes and moxifloxacin 0.1% into 21 eyes, endophthalmitis cases with positive cultures were generally related to organism resistance in cefuroxime eyes but to sensitive organisms in moxifloxacin eyes where the doses may have been insufficient in eyes with a larger postoperative anterior chamber volume.

The National Accreditation Board for Hospitals & Healthcare Providers guidelines have stressed the importance of proper infrastructure and comprehensive measures and protocols for preventing nosocomial infections. Although conventional Split Air Conditioners are acceptable in entry level accreditation of a small healthcare organization, Air Handling Units (AHUs) are mandatory for full accreditation. However, it is important to factor that they increase the capital cost substantially.



Indoor air quality is of utmost importance in the operating room where there should be no known contaminants at harmful concentrations. Several measures are mentioned to reduce the microbial load of air in the Operation Theatre (OT).

Minimum Efficiency Reporting Value rated filters, for example, High Efficiency Particulate Air filter, ensure clean ventilation in the OT through an AHU. In an AHU, clean, cooled, and dehumidified air is passed through a series of filters which include a 20-micron prefilter with 90% efficiency, a 5-micron fine filter with 95% efficiency, and a terminal High Efficiency Particulate Air filter with 99.97% efficiency. The suction side of the AHU will have a damper arrangement (valve) to draw fresh air during each recycling stage. Laminar air flow units which provide positive pressure ventilation above the operating area significantly reduce the bacterial colony forming units in the surgical field, but some studies question the efficiency of such units in preventing sepsis[4] in a statistically significant manner. In a systematic review and meta-analysis of 1947 records of orthopedic, abdominal, and vascular surgeries, no benefit of laminar airflow as compared to turbulent ventilation was found in reducing the risk of surgical site infection in total hip and knee arthroplasties and in abdominal surgery.

Germicidal Ultra Violet (UV) lights which emit UV-C radiations (253.7 nm) are bactericidal. However, those below 240 nm will produce Ozone which is toxic to the personnel inside the OT. Exposure to UV radiation can produce erythema of skin and painful keratoconjunctivitis. UV lights installed in rooms and even in the air ducts and split ACs can help in supplying clean air. The bactericidal effect of UV light is dependent on the irradiation dose and dwell time (the time the particle is exposed in the killing region of the radiation). Hence, proper

planning should be made on the wattage and number of lamps to be installed in the desired area.

Magnetized air media filtration (Electrostatic filters) can filter the indoor air. Germicidal lamps create positive-charged and negative-charged oxygen molecules which act like hydroxyl radicals and can destroy the cell wall of microbes. Photocatalytic oxidation occurs, releasing hydroxyl radicals when UV light and ambient light falls on surfaces sprayed with titanium dioxide (Nano TiO2). Hydroxyl radicals thus created harm the microbes.

Sterilizing instruments and linen are of utmost importance in reducing endophthalmitis. Steam under pressure is the most economical and effective method to sterilize items that are heat-resistant. Class B autoclave is a steam sterilizer that uses a vacuum pump to remove air/steam mixtures from the chamber prior to the beginning of sterilization. This process can remove 99% of the air inside of the chamber before the temperature and pressure increases to its stipulated parameters. Class B autoclave is the ideal one for use, whereas N type which has no vacuum pump can only be used as an auxiliary unit. Ethylene oxide sterilization can be used for heat-sensitive items like rubber and plastic. Sharp instruments are also best sterilized by ethylene oxide. It is always better to have sufficient sets of surgical instruments for the day's surgery rather than sterilize used ones in between cases. A slight increase in capital cost to have enough surgical sets is worth the investment.

There should be a disinfection protocol for every hospital. Daily cleaning and weekly cleaning procedures should be properly supervised. The right disinfectants at the right dilution must be used in the right way to clean surfaces. One cannot underestimate the role of periodic training to the OT staff to inculcate the correct attitude and work ethic in the practice of the infection control protocols. Properly designed operation theater complex will ensure that there would not be mixing up of clean and dirty linen and materials. The traffic inside the OT should be streamlined so that there is no entry of staff and patients from unclean environment to clean zones. Staff at all hierarchies should develop a habit of religious adherence to OT discipline. OT is one area where there should be zero tolerance in implementing correct techniques of asepsis. With the recent trend of eye hospitals getting themselves accredited by National Accreditation Board for Hospitals & Healthcare Providers, there has been a shift in the mindset of managements and staff to develop the right infrastructure and protocols for control of nosocomial infections.

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A mother's perspective on balancing family life, science, and ophthalmology



As ophthalmologists, we are constantly on the move. Many of us have a tight weekly circuit of hustling between clinics and the operating theater, meeting rooms – and as a clinician-scientist, frequent trips to the lab. Apart from the daily grind, there are also additional ad hoc teaching commitments and regional or international meetings to attend. With all this running about, it is sometimes difficult to ensure that the people who matter the most to us are not left behind. How do we keep things moving in the right direction both at work and at home? Sometimes one gets the sense that the right and left foot are separately planted on two flimsy rafts floating towards opposite banks of the river.

Perhaps a philosophical rather than a mathematical approach would be helpful to make sense of this balancing act. Aristotle may have suggested that "many things… are not merely a complete aggregate but instead some kind of a whole beyond its parts". Accordingly, my hope is that even if our individual efforts in each realm fall short of perfection, they will somehow coalesce into a worthwhile entity instead of a mass of discrete imperfections. Anyone who has ever marveled at the rabid scrawling of a child's first piece of "art" might be able to relate!

Having said that, we still strive for perfection at work and often also at home. The exhausting thing is trying to give your best at all times. Someone allegedly said, "if you find a job you love; you will never have to work again." This person probably never held a real job, but there is some truth in it. Falling in love is always the easy part; staying in love is hard work. This is true of most relationships, including the one we have with our job and sometimes even our family! Do we recall what it was like when we first set eyes on our spouse or cradled a little one, the uplifting joy and warmth that fills us when we are around people whom we love? Perhaps it would be a stretch too far to liken ophthalmology or scientific discovery to a similar experience, but we might recall the feeling of wonder and accomplishment the very first time we performed cataract surgery or caught a glimpse of the optic disc looking like a plump pink sunset. I still remember how my heart leapt with excitement when I saw that the little blobs in the cell culture plates that I had painstakingly prepared over several months had finally turned into recognizable retinal ganglion cells – and how beautiful they were to behold, unlikely anything I had ever seen in the clinic before.

Sometimes we need our families to remind us of how great it is to have the job that we do. The one time my husband watched a teaching video of phacoemulsification over my shoulder he commented that "it looks like you remove the clouds from people's eyes" which I thought was quite poetic. Of course, the next video happened to be about orbital decompression, which made him vow never to sneak a peek ever again ("oh my eyes!"). Family members and good friends are also essential in rallying around you when the experiment in the lab fails for the umpteenth time, or when you are faced with yet another rejection for that manuscript you spent many sleepless nights preparing – they remind you that while your worth is not tied to the meaning of your work, your work is still meaningful so persevere and do not give up!

Where our own efforts fail, we have to trust others. Functional magnetic resonance imaging (MRI) studies have discovered greater local connectivity in female brains as compared to male brains; this implies that women are better multi-taskers but concurrently also capable of worrying about a million things at the same time. Reminding myself not to fret about whether my husband remembered to pick up the milk on his way home, or if we packed extra diapers before dropping my child off at playgroup, or if my parents managed to keep their medical appointments is key to surviving to the end of a busy clinic or operating list. It is helpful to recognize that while we often feel like we are struggling against the tide of mounting work, there are many others who lend their support to aid our success: our colleagues, spouses, and caregivers who mind our beloved children or ailing parents. Another crucial

element is the big serving of grace that we need to bring to work every day. It is okay if your kid had to be wiped down with paper towels from the toilet dispenser after her shower at playgroup because her negligent parents forgot to pack her towel, no sweat if the kitchen sink is still clogged from the morning because the plumber could not find the time to drop by; never mind that the appointments staff accidentally booked another eight patients into your already packed list. Just smile and tell yourself that tomorrow will be a better day - at least you have a wonderful family and a terrific job to come back to.

Finally, do not forget to pause. Amid the busyness, it is essential to stop and smell the figurative roses from time to time. As Longfellow once said, "learn to labour and to wait." Many of us function like well-oiled machinery when it comes to laboring, but are less adept at the "waiting" aspect of the game. Yet, it is perhaps just as important, if not more so, to be aware of when to slow down and make the most of what is in front of you. Take some time to clasp that grateful patient's hand, sip a coffee amid the data analysis, or trade a giggle with your nurses. Hug your loved ones often, and for no reason at all. Treasure every moment that you possibly can – for Art is long, and Time is fleeting!

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Review Article

Lifestyle modifications – A new dimension in glaucoma management

ABSTRACT

Glaucoma, a neuro-degenerative disease of the eye, is characterized by progressive retinal ganglion cell (RGC) degeneration and a characteristic pattern of visual field loss. Despite a better understanding of the complex pathophysiology of glaucoma in the recent years, reduction of intra-ocular pressure (IOP) remains the primary outcome of different strategies of glaucoma management – medical, laser, or surgical. However, existence of various non-IOP-dependent mechanisms have broadened the targets as well as scope of glaucoma management. Lifestyle modifications have been a supplement in the management of different chronic diseases such as diabetes and hypertension. This option has been explored for glaucoma as well. Existing evidence suggests that some modifications in dietary habits, exercise, yogasanas, sleep postures, and so on have an influence on the underlying pathophysiology of glaucoma development as well as its progression. Increasing interest to investigate the potential of lifestyle modifications in glaucoma as preventive or supportive medicine in glaucoma management forms the basis of several recent research. This review aims to provide a comprehensive overview of the existing evidence relating the effect of different lifestyles, namely, dietary habits, supplements, exercises on IOP), and ocular perfusion pressure (OPP), which ultimately lead to retinal ganglion cell loss and optic neuropathy. Present knowledge indicates the presence of therapeutic potential in various lifestyle modifications over glaucomatous optic neuropathy. Although some findings are conflicting, there is a need for further exploration with well-structured clinical trials.

Keywords: Alcohol and glaucoma, caffeine and optic nerve, glaucoma and diet, glaucoma and exercise, IOP and exercise, OPP and exercise

INTRODUCTION

Glaucoma, a major ocular neuro-degenerative disease, is the leading cause of irreversible blindness in the world.[1] Its prevalence was 76 million in 2020 worldwide, and the global burden is expected to increase up to 118.8 million in 2040.[2] It is a multi-factorial disease with complex pathophysiology which ultimately leads to the apoptosis of retinal ganglion cells (RGCs) and optic nerve fibres. It causes an irreversible optic neuropathy with a characteristic pattern of visual loss.[3,4] Mechanisms behind the accelerated rate of RGC damage can be multiple, which includes vascular dysregulation, oxidative stress, immune-inflammatory response, excitotoxicity, and mitochondrial impairment.[5] IOP, increasing age, positive family history, and epigenetic and environmental factors are well recognized risk factors for glaucoma.[6] Among these, the most important risk factor is elevated IOP. Hence, all current standard therapies primarily aim to lower eye pressure with a combination of topical anti-glaucoma medications, laser therapy, and surgical intervention.[7] However, recent insight into newer dimensions underlying the pathophysiology of glaucoma suggests the role of various non-IOP-dependent factors. It has been reported that besides raised IOP, decreased ocular perfusion pressure (OPP) can lead to the death of RGCs and adjacent cells such as astrocytes and oligodendrocytes, initiating a vicious cycle of apoptosis cascade.[8] This knowledge has incited interest

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in exploring factors that affect the OPP as additional therapeutic modality that might be called as alternative or complementary medicine in glaucoma management.[8,9] This includes development of novel pharmacological agents as well as investigating non-pharmacological means such as lifestyle modifications with the capability of counteracting the degenerative process, maintaining optimal ocular blood flow, and providing neuro-protection.[10] These additional mechanisms can work either independently in glaucoma suspects as preventive measures or complementary to the IOP-based treatments in confirmed glaucoma cases. It aims at preventing further degeneration of RGCs and other neuronal components and to arrest the progression of disease. Certain lifestyles such as eating habits, sleep preferences, habits of meditation, yoga postures, and other exercises are known to have an influence over the pathophysiological mechanisms underlying glaucoma development and progression.[11] This aspect of the disease seems interesting and has recently gained interest with many published literature studies with conflicting opinion.[11,12] A thorough literature search was performed in PubMed, Google Scholar, and Scopus for relevant articles published in English with key words such as glaucoma and lifestyle, optic neuropathy and nutritional supplements, exercise and optic neuropathy, exercise and IOP, diet and glaucoma, body weight and glaucoma, and sleep postures and IOP. Existing reports signify therapeutic potential in various lifestyle modifications in glaucoma patients. Furthermore, this area has tremendous research potential that needs to be explored and validated by well-planned randomized control trials (RCTs). In this review, we provide a summary of the current evidence on the effect of different lifestyles, dietary habits, and supplementations on the incidence and progression of glaucoma and their future prospects in the management of glaucoma.

RELATION OF DIET, DIETARY SUPPLEMENTS, AND GLAUCOMA

Essential nutrients and glaucoma

Different components of food such as carbohydrates, proteins, essential fats, vitamins, and minerals have been evaluated for their association with glaucoma in different study designs [Table 1]. Kang *et al*.,[13] in a prospective study on health professionals, demonstrated a lower risk of primary open-angle acute glaucoma (POAG) with diet rich in nitrate contents such as green leafy vegetables. Hanyuda and colleagues, in three cohort studies, showed that low-carbohydrate diets were not associated with the risk of POAG, but higher consumption of fat and protein from vegetable sources substituting for carbohydrates was associated with a lower risk of the POAG sub-type with initial paracentral VF loss.[14] A cross-sectional study in elderly females concluded that higher intake of certain fruits and vegetables high in vitamins A and C and carotenoids may be associated with a decreased likelihood of glaucoma. However, another case control study showed that intake of fruit juice, low-salt diet consumption, and low-fat content meat can be beneficial for glaucoma suspects and POAG patients.[15,16] In general, it has been found that dietary modifications such as restricting saturated fats, salt, and sugar recommended for a good cardio-vascular status are beneficial for ocular health as well.[17]

Poly-unsaturated fatty acids and glaucoma

The role of poly-unsaturated fatty acids (PUFAs), particularly long omega-3 fatty acids (ω-3 PUFAs) in glaucoma, has recently been investigated. This is because patients with POAG have an abnormal blood fatty acid composition that is characterized by a reduction in eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and omega-3 fatty acids.[18,19] In a survey conducted by the National Health and Nutrition Examination, it was found that increased daily dietary intake levels of EPA and DHA were associated with a lower likelihood of glaucomatous optic neuropathy, but high consumption of total PUFAs was associated with a higher risk of glaucoma. Hence, it was assumed that increasing the proportion of dietary ω-3 consumption levels while controlling overall daily PUFA intake may be protective against glaucoma by reducing oxidative stress and inflammation.[20] Oral DHA or omega-3 supplement has finally been approved as adjunct therapeutics for reducing IOP in normotensive adults and pseudo-exfoliation glaucoma patients.[21,22]

Vitamins, minerals, and glaucoma

Oxidative stress leading to apoptosis of RGCs is an established pathophysiology underlying glaucoma.[23] Hence vitamins such as Vit A, C, and E, which are known to have anti-oxidative properties, have been hypothesized to provide neuro-protection by reducing the oxidative stress. Few epidemiologic studies and small randomized clinical trials have been conducted to explore the association of vitamins with glaucoma with conflicting results. Yuki and co-workers investigated the levels of anti-oxidant vitamins, A, B_9, C, and E, and the anti-oxidative substance uric acid in the serum of Japanese patients with normal-tension glaucoma (NTG) and compared the results with normal controls.[24] It was found that NTG patients had lower serum levels of vitamin C and increased levels of uric acid. Another survey by Wang *et al*.[25] noted that neither supplementary consumption nor serum levels of vitamins A and E were associated with glaucoma prevalence, but supplementary consumption of vitamin C was associated with a decreased odds ratio of glaucoma; however, serum levels of vitamin C did not correlate with glaucoma prevalence. The use of multi-vitamins or supplements of vitamins C, E, and A

in any dose or duration, analyzed by a large prospective cohort study, was unrelated to POAG risk.[26] It has been shown in various recent studies that neuro-degenerative diseases such as Alzheimer dementia, Parkinson's disease, depression, and schizophrenia aggravate the progression or elevate the incidence of glaucoma.[27] Since Vit D has been associated with such neuro-degenerative diseases, its role in IOP control has also been evaluated.[28] Krefting *et al*.,[29] in a small, randomized controlled trial in healthy participants, found no associations between serum 25-hydroxyvitamin D [25(OH) D] levels and IOP. Even supplementation of vitamin D3 to participants with low levels of 25(OH) D did not affect the IOP. Hence, these results do not support the role of vitamin D in IOP regulation.

Engin *et al*.[30] investigated the neuro-protective role of α-tocopherol and demonstrated enhanced ocular blood flow which was time- and dose-dependent. The additional vaso-regulatory effect of the antioxidant α-tocopherol on retina was via the protein kinase C pathway. Contrary to this, no statistically significant effect on the success rate of trabeculectomy was found when oral α-tocopherol was given post-operatively by Goldblum and co-workers.[31] The supplement of nicotinic acid in the amide form in mice study shows protection against glaucoma, but in humans, the relation is yet to be explored. However, there are some studies showing a decreased serum level or reduced intake of retinol equivalents and vitamin B1 and increased intake of magnesium with an increased risk of OAG.[32-34] Besides magnesium, some studies show an increased risk of glaucoma with a high level of calcium, iron, and selenium because of increased oxidative stress.[35-37]

Herbal medicine and glaucoma

Herbal medicines containing flavonoids and polyphenols such as Ginkgo biloba (GBE), saffron, and anthocyanins are increasingly being used in glaucoma patients. They are thought to decrease the oxidative stress, enhance ocular perfusion, and provide neuro-protection as well.[38] Although animal models have shown favorable outcomes in preventing RGC loss, human studies document conflicting results.[39] A randomized, placebo-controlled, crossover study by Quaranta *et al*.[40] reported statistically significant improvements in visual field indices in patients receiving GBE as compared to the placebo group. However, IOP was similar in the two groups. A randomized clinical trial by Park *et al*. reported that GBE significantly increases peri-papillary blood flow in patients with NTG compared to placebo.[41] On the contrary, study conducted by Guo and colleagues reported improvements neither in visual field indices nor in contrast sensitivity in GBE-treated groups compared to placebo.[42] Bonyadi *et al*.[43] investigated the hypotensive effects of saffron extracts in clinically stable POAG patients receiving treatment with timolol and dorzolamide eye drops. The ocular hypotensive effect became evident after 3 weeks of therapy with oral aqueous saffron extract. Anthocyanins, a kind of polyphenols abundant in berries such as black currant, have anti-oxidant and anti-inflammatory effects.[44,45] A randomized, placebo-controlled trial by Ohguro and co-workers demonstrated significantly decreased deterioration of visual field mean deviation and increased ocular blood flow of OAG patients with BCAC supplement compared to placebo-treated ones, but there was no change in IOP.[44]

RELATION OF EXERCISE AND GLAUCOMA

Dynamic exercise and glaucoma

Physical exercises have an important role in maintaining health and well-being of an individual. Their benefits are well studied in a wide range of systemic and ocular diseases, including glaucoma.[46] Lowering IOP, increasing ocular perfusion, and providing neuro-protection form the cornerstone of glaucoma management. The impacts of physical exercise on IOP, ocular perfusion, neuro-protection, and mental health in patients with glaucoma have extensively been investigated in the recent past.[47,48] Existing literature reports a consistent decrease of IOP after dynamic exercises such as cycling, walking, jogging, and stepping with a wide range of variations from 0.56 mmHg to 5.6 mm Hg.[49,50] The amount of IOP reduction depends upon the type, intensity, duration of the exercise, current general fitness of the patient, and existing ocular pathology. A meta-analysis by Roddy *et al*.[51] suggests an almost double IOP reduction effect in sedentary persons compared to their active counterparts. Studies have been performed to find if there is any difference in dynamic exercise on glaucoma patients as compared to healthy individuals.[52] Surprisingly, Qureshi *et al* have reported in 1995 that the magnitude and duration of exercise-induced IOP reduction could be more prominent in patients with glaucoma not receiving treatment, compared to normal subjects.[53] A study by Yokota *et al*.[54] in 1996 showed that self-reported habitual exercise of more than 30 minutes per week was associated with slower visual field progression in open-angle glaucoma patients. Exercise-induced IOP reduction in patients with glaucoma was independent of the use of anti-glaucoma agents. Yang *et al*.[55] have reported that IOP reduction after dynamic exercise is more profound in myopic eyes as compared to emmetropic eyes, probably because of insufficient perfusion to the choroid and the retina that might result in a defective auto-regulatory response. Furthermore, the magnitude of IOP reduction increases with the intensity of exercise but not with the duration.[56]

Although the underlying mechanism of IOP reduction remains uncertain, it has been postulated to be related to nitric oxide release. There is shifting of the blood flow to the muscles and the raising of plasma osmolality with blood lactate decreasing blood pH.[46,47] The effect seemed to wear off shortly with time, and the IOP-lowering effect was only modest in most of the reports.[46,49] The long-term effect of exercise on sustainability of IOP remains an area of research.

Certain forms of glaucoma such as pigment dispersion glaucoma (PDG) respond to the contrary where exercise may cause remarkable IOP elevation in exercise-induced iris concavity and enhanced pigment release.[57-59] Likewise, certain types of dynamic exercise can adversely affect the ocular health. Several case reports exist that document activities such as swimming with goggles, scuba diving, and Bungee jumping, which can cause visual impairment and visual field defects because of either raised IOP or ocular barotrauma.[60-63] This adverse effect is more prominent in glaucoma patients.[63]

Isometric exercise and glaucoma

Exercises performed in static positions, such as weightlifting and hand gripping, are called isometric exercises. Although there is a decrease in IOP after dynamic exercise, the effect of isometric exercise on IOP is controversial. Castejon *et al*.[64] have documented a rise in IOP after isometric exercise in both humans and animal studies. Vieira *et al*.[65] reported this IOP elevation to be related to the Valsalva maneuver that increases the episcleral venous pressure. Discontinuation of the Valsalva maneuver could partly relieve the raised IOP. Another study by Rüfer *et al*.[56] found that there was no influence of isometric exercise on IOP if a Valsalva maneuver was avoided.

Yoga is a popular exercise in India but practiced worldwide with great enthusiasm and anticipation as a viable alternative to conventional medical management for different ailments.[66] Some of the Yoga positions can be regarded as isometric exercises. Yoga postures (yogasanas) that involve body inversion were found to have a severe impact on IOP. Baskaran *et al*.[67] in 2006 demonstrated an immediate 2-fold increase (around 15 mmHg) in IOP while performing Sirsasana, which is a headstand posture. The IOP returned to near baseline level as soon as the sitting posture was resumed. Evidence suggests that the transient IOP elevation in Sirsasana contributes to disease progression in patients with glaucoma. The rise in IOP in four common head-down Yoga positions, namely, Adho Mukha Svanasana, Uttanasana, Halasana, and Viparita Karani, is well reported. The range of IOP elevation reported varies from 16% to 70% in both patients with POAG and normal subjects.[68] Postulations behind this rise include an increase in choroidal thickness in addition to the increase in episcleral venous pressure.[68,69] In the head-down position, there is an increase in intra-cranial cerebrospinal fluid pressure, which indirectly influences the choroid veins draining into superior ophthalmic vein and finally into intra-cranial cavernous sinus.[69,70] Hence, these head-down postures might be a risk factor for glaucoma progression and should be avoided in people with or at high risk of glaucoma.[70,71]

Exercise and ocular perfusion pressure

As per the recent insight into the pathophysiology of glaucoma, besides IOP, ocular perfusion pressure (OPP) also forms an important determinant of optic nerve health.[72] Evidence from epidemiological surveys suggested that subjects with low OPP were more likely to develop glaucoma and suffer from disease progression.[73] Published research studies are consistent with the fact that physical exercise remarkably induces OPP elevation. The association between OPP and ocular blood flow (OBF) to the posterior pole of the eye is complex because of the presence of auto-regulation, a mechanism that maintains constant blood flow despite changes in OPP.[74] Auto-regulation occurs in both dynamic exercise and isometric exercise, resulting in the unparalleled elevation of OBF and OPP. Contrary to the different responses of IOP to dynamic exercise and isometric exercise, the OPP was elevated in both, although the increase was limited because of auto-regulatory response.[75]

Neuro-protection and physical exercise

Limited but consistent evidence of neuro-protection from exercise in animal models has been found in various retinal degenerative diseases, although the type and protocol of exercise were inconsistent and not comparable in those studies.[76-78] Possible underlying mechanisms of exercise-induced neuro-protection include up-regulating neurotrophin expression, such as brain-derived neurotrophic factor (BDNF), enhancing mitochondrial functions and reducing inflammation.[79,80]

Mental health in glaucoma and exercise

The role of exercise in mental health has been widely studied. An increase in physical activity is directly correlated with a decrease in anxiety and depression by De Moor *et al*.[81,82] A recent study by Lim and colleagues from Singapore has reported the incidence of anxiety and depression in patients with glaucoma to be as high as 64% and 30%.[83] The mental disorders not only have a negative impact on the quality of life of patients but also promote disease progression. Mental stress was found to increase

IOP and induce insomnia by Marc *et al*. Surprisingly, the use of zolpidem, a drug to treat insomnia, was found to increase the risk of glaucoma development.[84,85] Contrary to this, mindful meditation reduces stress, decreases IOP, and promotes ocular health.

In addition to preventing RGC loss via IOP control and increasing ocular perfusion, exercise may be beneficial in enhancing the overall well-being of patients with glaucoma and thus improving their quality of life.

BODY MASS INDEX AND GLAUCOMA

Although obesity has been associated with higher IOP, contrastingly, Lin *et al*.[86] have reported association of a lower BMI, especially in women in the 40–49 age range, to a higher incidence of NTG. It has been observed that female patients with a lower BMI developed more paracentral visual defects compared to patients with a higher BMI.[87] The impact of sudden weight loss on IOP, especially through bariatric surgery, was investigated in some studies. Lam and co-workers reported that each 10 unit decrease in BMI correlates with a 2.4 mm Hg decrease in IOP.[88,89]

CAFFEINE, ALCOHOL, CANNABINOIDS, SMOKING, AND GLAUCOMA

Caffeine, a methylxanthine alkaloid, consumed worldwide in different beverages, has been reported to cause a transient rise in the IOP and OPP levels in both healthy individuals and glaucoma patients.[90,91] This action is basically attributed to increased intra-cellular levels of cyclic AMP and increased hydrostatic pressure, which cause aqueous humor over-production. Further raised cyclic AMP results into decreased outflow by the relaxation of smooth muscle tone.[92,93]

Relationship between alcohol intake and glaucoma is not yet clear. Some studies show no association between the two, whereas few cohort studies have reported a positive relationship between alcohol intake and an increase in IOP. These mixed findings may be attributed to individual differences in alcohol metabolism that can affect IOP and the ganglion cell complex.[94]

Tobacco consumption, in general, is potentially detrimental for health. Although nicotine potentially increases blood flow, its effect on optic nerve blood flow remains conflicting. Some studies have reported the neuro-protective effect of nicotine on the retina, preventing glutamate-induced excitotoxicity in RGC.[95] On the other hand, it has vasospastic properties as well, which may cause glaucomatous nerve damage by decreasing blood flow. The difference in results can be attributed to multiple mechanisms of action of nicotine. Almost all studies have shown a decrease in IOP with topical, inhaled, or intravenous cannabinoids with strong evidence of neuro-protection in animal studies. Both increases and decreases of IOP have been reported as a function of the mode of administration and of the precise cannabinoids used.[96]

Sleep posture and glaucoma

Change in body posture causes change in IOP and OPP. Studies conducted to investigate the effects of different sleeping positions of the head and body in healthy subjects reported an elevation of IOP as compared with the sitting position.[97] Postural change from supine to lateral decubitus or prone with the head turn position increased the IOP of the dependent eyes without significant alteration in OPP.[98] Although in pigment dispersion glaucoma, lateral and prone sleeping positions usually result in significant elevations of IOP, it was unrelated to the dependency status. In general, use of specially designed pillows and bed-head elevation up to 30 degrees are recommendations to avoid IOP rise while sleeping.[99]

ELECTRONIC GADGETS AND GLAUCOMA

Mobile devices (i.e., smartphones) have become an integral part of daily living in today's era. Published research reports that reading and writing on smartphones cause a significant increase in IOP.[100] The elevation was faster and greater under low-light conditions. The exact underlying ocular dynamics for these IOP changes during and after smartphone work are unclear. However, the mechanism postulated for this change relates to the phenomena of accommodation and convergence with external ocular muscle (EOM) contraction. In addition to this, psycho-physiological stress-associated dry eye and neck-flexion posture also contributes for a rise in IOP.[101]

CONCLUSION

Modifications in the lifestyle do seem to have a positive impact on the health of the optic nerve. It includes our physical activity, exercises, eating habits, and even addictions to smoking, alcohol, or use of electronic gadgets [Table 2]. They have the potential to modulate the IOP and OPP and hence can be explored as an alternative or complementary medicine to the existing plan of glaucoma management. Although some of the existing pieces of evidence are contradicting and insufficient to make strong recommendations, they need to be validated by well-structured randomized trials.

Table 1: Summary of association of nutrients and glaucoma

Authors	Study population	Study design	Study object	Observation
Yoserizal *et al*., 2019	581 participants, 61 of whom were diagnosed with glaucoma	Cross-sectional	Associations of nutrient intake on glaucoma	High intake of iron or low intake of vitamin A and vegetable fat were associated with an increased risk of glaucoma
Wang *et al*., 2018	3865 participants in NHAN	Cross-sectional	Daily dietary intake of poly-unsaturated fatty acid (PUFA*), including ω-3 fatty acids	Increased daily dietary consumption levels of EPA and DHA were associated with lower likelihood of glaucomatous optic neuropathy. However, consumption levels of total PUFAs in the higher quartiles were associated with a higher risk of glaucoma, which may have resulted from relative intakes of ω-6 and ω-3 fatty acids and other confounding co-morbidities. In general, increasing the level of dietary ω-3 while controlling consumption of total daily PUFA intake may be protective against glaucoma
Kang *et al*., 2016	104,987 subjects	Prospective cohort	Dietary nitrate intake, derived from green leafy vegetables	Higher dietary nitrate and green leafy vegetable intake inversely associated with glaucoma risk. Incident self-reported open-angle glaucoma
Wang *et al*., 2013	2912 participants (≥40 years)	Cross-sectional	Vitamins A, C, and E intake and serum level	Only supplementation of vitamin C was found to be associated with decreased odds of glaucoma prevalence
Ramdas, *et al*., 2012	3502 adults (≥55 years)	Prospective cohort	Dietary anti-oxidants (carotenoids, vitamins, and flavonoids) and nutrients influence the blood flow (omega fatty acids and magnesium	Incident POAG*, detected by visual field testing. People with an equivalent intake of vitamin A ($P=0.01$) or vitamin B1 ($P=0.03$) are associated with an about twofold lower risk of OAG* compared to those with a low intake of these nutrients, and people with a high intake of magnesium have an about threefold increased risk of OAG
Giaconi *et al*., 2012	584 female subjects	Cross-sectional	Dietary fruits and vegetables containing different vitamins	Higher intake of vegetables and fruits rich in vitamin A and vitamin C was associated with a lower likelihood of having glaucoma
Park *et al*., 2011	30 patients with NTG	Randomized controlled trial	Gingko biloba extract (80 mg twice a day) or placebo	A statistically significant increase in blood flow at almost all points was observed (except for the superior nasal peri-papillary area), in comparison to the placebo, without noticeable changes in VF indices
Quaranta *et al*., 2003	27 patients with NTG (with or without treatment)	Randomized controlled trial	Ginkgo biloba extract 40 mg, 3 times/day or placebo	VF indices improve significantly without changes in IOP
Bonyadi *et al*., 2014	34 POAG patients in 2 groups	Randomized controlled trial	Saffron extract 30 mg/day or placebo	A statistically significant IOP reduction was noted after 3 (10.9±3.3 mmHg in the saffron group as compared to 13.5±2.3 mmHg in the control group) ($P=0.013$) and 4 weeks (10.6±3.0 versus 13.8±2.2 mmHg) ($P=0.001$) of treatment
Ohguro *et al*., 2012	38 patients with OAG (in 2 groups: treated and placebo)	Randomized controlled trial	Black currant antocyanoside extract 50 mg/day or placebo	Less VF mean deviation deterioration and increased ocular blood flow were seen in the treated group

*(2.6%)

Table 2: Modifications in lifestyle and their effects on glaucoma

Factors	Decreased risk	Increased risk
Diet	Low carbohydrate, low salt low saturated fat, (EPA and DHA), Vit A, C, B1, and E, green leafy vegetables Ginkgo Biloba, saffron extract,	Increased intake of iron, magnesium, and selinium
Exercise	Aerobic exercise, briskwalking, treadmill, mindful meditation	Excessive exercise, swimming with goggles, Scuba diving, Bunjee jumping, head stand/head down yogasanas (Sirsasanas, Adho Mukha Svanasana, Uttanasana, Halasana, and Viparita Karani)
BMI	BMI within a normal range	High BMI, Low BMI
Caffeine/Smoking/ alcohol		Cigarette smoking, increased intake of caffeine
Sleep posture	Bed head end elevation of 30 degree	Lateral decubitus and prone
Electronic gadgets		Mobile, laptop in low illumination

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Conflicts of interest

There are no conflicts of interest

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Christmas tree pattern in age related cataracts

A 66-year-old male presented in eye outpatient department for insidious onset-colored halos for a month. He, being a known case of Parkinsonism, was on treatment with Syndopa for the past 5 years. His visual acuity was OU 6/18–6/12. His anterior segment showed multiple polychromatic needle-shaped crystals traversing in all directions, located in the anterior nucleus of the lens in the right eye [Figure 1], the same being minimally visible in the left eye lens [Figure 2].

It was diagnosed as Christmas tree cataract (CTC), though an appropriate systemic association could not be demonstrated. From a review of such CTCs, mechanisms postulated for its occurrence vary from study to study.[1] While few studies suggest the opacities to be cholesterol crystals,[2] few say that they were most likely made of cystine crystals due to an age-related aberrant breakdown of crystallins induced by elevated Ca++ levels.[3] One study postulated the diffraction of light from parallel-sided stacks of fused cell membranes to be the cause for the striking polychromatic luster.[4]

CTC is very well associated with myotonic dystrophy (DM), wherein premature cataract (<55 years) with polychromatic crystals of the CTC in posterior lens capsule.[5] CTC has been identified as the first sign of DM, developing into full-blown symptoms of myotonia after 7–14 years.[6] An exhaustive search of PubMed literature did not show any association between CTCs and Parkinsonism or Syndopa usage. As noted, in the reported patient, the presence of CTC in anterior nucleus and in elderly age of 66 years does not fit into DM.

CONCLUSION

The Christmas tree cataract in this patient is probably age related. Had it been diagnosed in a young patient, the Ophthalmologist should take up the responsibility to refer promptly to a Neurophysician to rule out the possibility of DM.

Declaration of patient consent

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

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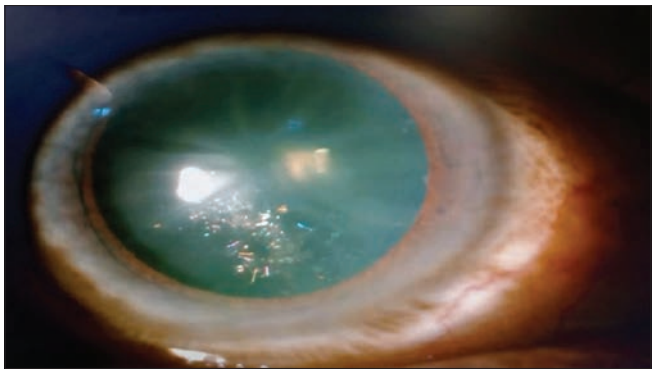


Figure 1: Right eye showing several polychromatic needle crystals occupying anterior nucleus of inferior part of lens giving it a decorated Christmas tree pattern

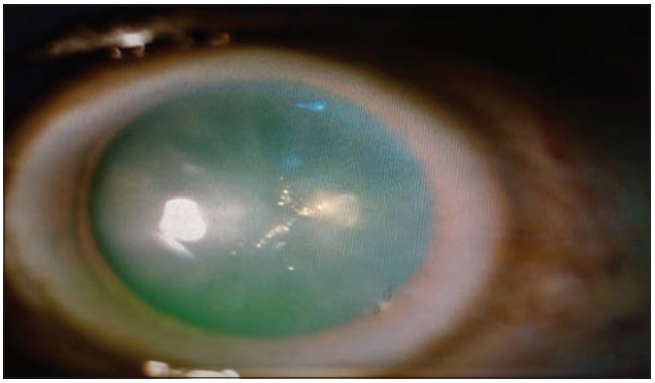


Figure 2: Left eye shows very few needle crystals in the center of lens

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Infectious scleritis: Clinical profile and treatment outcome in a tertiary eye care center in Southern India

ABSTRACT

Purpose: The purpose of the study is to study the clinical features, causative organisms, and treatment outcome in cases of infectious scleritis. **Design:** This is a retrospective study. **Materials and Methods:** Medical and microbiological records of all patients diagnosed as infectious scleritis between January 2016 and December 2019 were reviewed. Information including age, sex, clinical features, predisposing factor, causative organism, and treatment outcome was extracted from records and analyzed. **Results:** A total of 12 cases of infectious scleritis were identified. Five (41.6%) cases had a prior history of trauma and 3 (25%) cases had undergone cataract surgery in the past. Redness with pain in the involved eye was the most common presenting complaint (91.6%, *n* = 11). Most of the cases (*n* = 11, 91.6%) presented with visible scleral abscess under slit-lamp examination. Fifty percent cases (*n* = 6) were caused due to fungal infection, most common species being *Aspergillus* (41.6%, *n* = 5). *Pseudomonas aeruginosa* (25%, *n* = 3) was the second most common causative organism. Microbe-specific medical treatment was given and scleral debridement done for all the eyes. Globe was preserved in 83.3% (*n* = 10) of the eyes. About 41.6% (*n* = 5) of eyes had best-corrected visual acuity 6/18 or better at the end of 3 months. **Conclusion:** Previous history of trauma should raise high suspicion regarding infectious etiology in any case of scleritis. In cases with no antecedent history, subtle clinical differences between autoimmune and infective scleritis, along with response to therapy, should be kept in mind to reach at a diagnosis. In tropical countries like India, fungi, most commonly *Aspergillus flavus*, are the most common organism responsible for infective scleritis. Along with medical treatment, surgical debridement plays a major role in the management of infective scleritis.

Keywords: Fungal, infectious, scleritis, trauma

INTRODUCTION

Scleritis refers to a severe painful inflammatory condition of sclera, which may involve cornea, uveal tissue, and adjacent episclera. Scleritis due to infective etiology is a rare entity which accounts for 5%–10% of all cases of scleritis.[1] The initial clinical picture of infectious scleritis may be identical to that caused by immune-mediated scleritis. Therefore, in a patient presenting with scleritis, an infectious etiology is many a times not suspected resulting in unusual delay in the diagnosis and consequently worsened outcome. Infectious scleritis may follow accidental or surgical trauma, severe endophthalmitis, or may occur as an extension of a primary corneal infection.[2] Systemic illness, use of corticosteroid and immunomodulators, or previous history of scleritis may also be predisposing factor.[3] *Pseudomonas aeruginosa* has been the most commonly reported causative agent in various series followed by fungus.[4-6] Other causative organisms such as *Staphylococcus* species, *Streptococcus* species, haemophilus influenza, *Stenotrophomonas maltophilia, Serratia marcescens, Mycobacterium* species, *Nocardia,* fungus, and virus have also been reported.[3] However, reports from India have stated fungi to be more common in tropical regions.[1] Sclera being an avascular structure with dense collagenous framework

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limits the penetration of traditional topical antibiotics. The clinical outcome in cases of infectious scleritis is generally poor and most cases required evisceration in many series.[2,7] Furthermore, very often misdiagnosis of autoimmune scleritis or postsurgical inflammatory scleritis with vigorous corticosteroid regime worsens condition and delays timely intervention.[8] However, a review of more recent reports clearly suggests that infectious scleritis can be managed successfully with good visual and anatomical outcome as a result of early diagnosis with combined antibiotic therapy and early surgical intervention.[4-6]

MATERIALS AND METHODS

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

RESULTS

We included 12 cases (12 eyes) of infectious scleritis, among which 9 were males and 3 were females [demographic features, clinical presentation, and etiology are detailed in Table 1, treatment and outcome are detailed in Table 2]. Age ranged from 32 years to 76 years (mean 52.4 ± 13.3 years, median 49.3 years). The mean duration from onset of symptoms to presentation was 12.16 ± 9.5 days (range of 4–30 days). The mean follow-up period was 16.3 ± 14.4 weeks (range of 3–46 weeks). Average duration of healing of lesion with appropriate treatment was 4.9 ± 3.2 weeks (range of 1–12 weeks).

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

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

All cases underwent scleral debridement except one case with postcataract surgery wound melt [Figure 3]. Nearly 25% ($n = 3$) cases underwent multiple debridements due to recurrence at different location of sclera during the course of treatment. The surgical debridement was diagnostic in all cases. This also facilitated debulking

Table 1: Demographic features, clinical presentation, and etiology

Case number	Age/sex	Eye involved	Predisposing factor	Steroid use	Complains (days)	Associated features	Foci	Smear	Culture
1	48/male	OS	Trauma (sugarcane 1 month)	-	7	SA	Multifocal	Nocardia	*A. flavus*
2	60/male	OD	Trauma (stick 1 month)	Yes	30	SA	Unifocal	ND	*A. flavus*
3	40/male	OS	Cataract SX (6 years)	-	7	SA, scleral thinning, adherent leucoma	Unifocal	ND	*K. pneumoniae*
4	50/male	OD	Nil	Yes	4	SA, AC reaction	Unifocal	ND	*P. aeruginosa*
5	32/female	OS	Nil	Yes	5	SA	Unifocal	Fungus+GPC	*A. flavus, S. pneumonia*
6	68/male	OS	Trauma (insect 14 days)	-	14	SA	Unifocal	ND	*A. flavus*
7	36/male	OD	Trauma (insect 4 days)	-	4	SA, corneal scar	Unifocal	GPC	*S. epidermidis*
8	46/male	OS	Nil	Yes	7	SA	Unifocal	No organism	*Fusarium*
9	49/female	OS	Nil	Yes	7	SA, corneal infiltrate, AC reaction	Multifocal	ND	*P. aeruginosa*
10	60/male	OD	Trauma (dust 20 days)	-	20	SA, AC reaction	Unifocal	No organism	*Nocardia*
11	64/female	OD	Cataract SX (3 years)	-	30	SA	Unifocal	No organism	*A. flavus*
12	76/male	OS	Cataract SX (15 days)	Yes	11	Scleral melt, wound gaping, corneal infiltrate, AC exudates	Multifocal	GNB	*P. aeruginosa*

SA - Scleral abscess, ND - Not done, GPC - Gram-positive cocci, GNB - Gram-negative bacilli, OS - Oculus sinister, OD - Oculus dextrus, AC - Anterior chamber, *K. pneumoniae - Klebsiella pneumonia, A. flavus - Aspergillus flavus, P. aeruginosa - Pseudomonas aeruginosa, S. pneumonia - Streptococcus pneumonia, S. epidermidis - Staphylococcus epidermidis, SX - surgery*

Table 2: Treatment and outcome

Case number	V/A at presentation	Medical treatment (topical)	Medical treatment (systemic)	Surgical treatment	Final V/A	Complications	Outcome	Duration of healing (weeks)
1	6/18	Natamycin, itraconazole, amikacin	Amikacin, TMX-SMZ	SD*, cryo, evisceration	NPL	Absolute glaucoma, painful blind eye	Evisceration	-
2	6/24 p	Natamycin, gatifloxacin	Ketoconazole	SD*	6/24	Cataract	Resolved	12
3	6/60	Gatifloxacin	Amikacin	SD	6/24		Resolved	2
4	6/12	Gatifloxacin, amikacin	Amikacin	SD*	6/12 p		Resolved	6
5	6/6	Natamycin, moxifloxacin		SD	6/6		Resolved	1
6	5/60	Natamycin, gatifloxacin		SD	6/36		Resolved	2
7	6/60	Gatifloxacin, tobramycin	Ciprofloxacin	SD	6/24	RCS thickening, ST fluid, cataract	Resolved	2
8	6/12	Natamycin, moxifloxacin		SD	6/18	Cataract	Resolved	6
9	3/60 p	Amikacin, moxifloxacin	Amikacin	SD	4/60		Resolved	4
10	6/9	Amikacin, moxifloxacin		SD	6/9		Resolved	6
11	6/18 p	Natamycin, moxifloxacin		SD	6/18		Resolved	8
12	PL+	Amikacin, moxifloxacin	Amikacin	SPG, IOAB, E	NPL	Panophthalmitis	Evisceration	-

*Multiple debridements. TMX-SMZ - Trimethoprim sulfamethoxazole, IOAB - Intraocular antibiotics, SPG - Scleral patch graft, SD - Scleral debridement, RCS - Retina-choroidal-scleral, NPL - No light perception, ST - Subtenon

of the infected scleral tissue and improved the drug penetration. During the surgical debridement, the actual area of involvement was usually found to be larger than that visible on slit-lamp examination. One case (Case 12) with post small incision cataract surgery scleral wound melt received scleral patch graft as primary procedure along with intraocular antibiotic in view of suspected postoperative endophthalmitis.

All cases with proven fungal etiology were treated with topical natamycin and topical fluoroquinolones, with additional systemic antifungal, in case of poor response. All cases due to culture-proven bacterial etiology were treated with topical antibiotics and systemic medication, based on antibiotic susceptibility testing [Table 3]. All cases of proven Pseudomonas infection received intravenous amikacin, while staphylococcal infection received oral ciprofloxacin. Tapering doses of topical steroids were given in scleritis of bacterial etiology after active infection subsided. Eighty-three percent (n = 10) of cases had complete resolution of infection and globe architecture was preserved, while 2 eyes underwent evisceration. Posterior segment examination with B scan was normal in all the eyes except one eye with panophthalmitis (Case 12).

Table 3: Antibiotic susceptibility of isolated organisms (Kirby-Bauer disc test)

Serial number	Case number	Organism	Antibiotic susceptibility							
			Chloramphenicol	Cefazolin	Vancomycin	Ciprofloxacin	Gatifloxacin	Ofloxacin	Amikacin	Tobramycin
1	3	*Klebsiella*	Resistant	ND	ND	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive
2	4	*Pseudomonas*	Sensitive	ND	ND	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive
3	5	*S. viridans*	Sensitive	Resistant	Sensitive	Sensitive	Sensitive	Sensitive	ND	Sensitive
4	7	*S. aureus*	Sensitive	Resistant	Sensitive	Sensitive	Resistant	Sensitive	ND	Sensitive
5	9	*Pseudomonas*	I	ND	ND	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive
6	10	*Nocardia*	Resistant	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive
7	12	*Pseudomonas*	Sensitive	ND	ND	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive

ND - Not done, *S. viridans - Streptococcus viridans, S. aureus - Staphylococcus aureus*

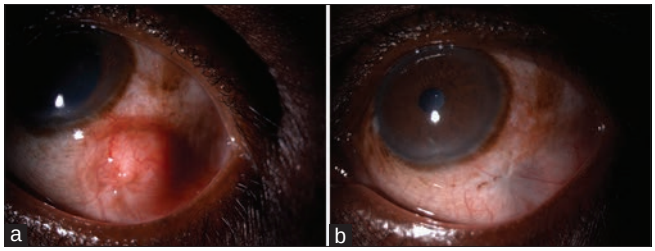


Figure 1: (a) Unifocal scleral abscess of fungal etiology (Case 8). (b) Unifocal scleral abscess 2-month posttreatment (Case 8)

Among the eyes which underwent evisceration, one patient (Case 1) [Figure 4] with culture-proven fungal infection, showed poor response with antifungal treatment, progressed to develop secondary glaucoma and painful blind eye and had to be eviscerated. Another case (Case 12) with postcataract surgery scleral melt underwent scleral patch graft and intravitreal antibiotics, subsequently developed panophthalmitis and was eviscerated. Three (25%) cases resolved with progression of cataract while one among them was complicated with choroidal detachment during the course of treatment which resolved with oral steroids.

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

DISCUSSION

As reported earlier, trauma or prior history of ocular surgery raises the suspicion of infectious scleritis in all cases of scleral inflammation presenting as scleral abscess or ulceration.[1,5,9] Pterygium excision has been reported to be the most common surgical procedure in many series.[4-6,10] Cataract surgery was seen to be the most common in another series.[1,9,11] In our series, 50% cases had trauma while 25% cases had history of cataract surgery, while no case of prior pterygium surgery was seen. This difference of more number

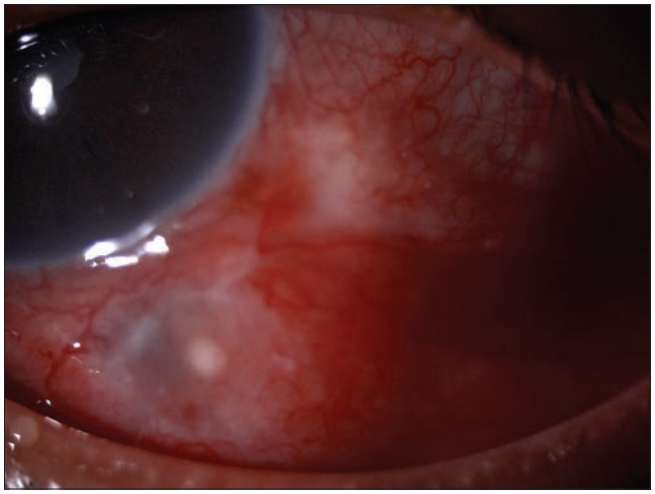


Figure 2: Unifocal scleral abscess progressing to multifocal scleral abscess after initial debridement (Case 2). Scleral abscess progressing to multifocal scleral abscess after initial debridement (Case 2)

of cases due to trauma may be due to rural and agricultural background of our patients. Compared to rest of the world, small incision cataract surgeries are more often performed in India, which accounts for it being the most common ocular surgery responsible for the same.[9] It is unusual for the scleral site to be infected long after surgery but surgical-induced necrotizing scleritis (SINS) has been seen to be activated long after surgery.[12] Lin *et al*.[6] postulated that after initiation of SINS, microorganisms caused late-onset postsurgical infective scleritis. One of the cases in our series had post-SICS wound melt with infiltrate (Case 12). Melt in this case may be attributed to infective agent rather than SINS. None of our patients with late-onset scleritis had systemic vasculitis. Similar experience was reported by Altman *et al*.[13] and Jain *et al*.[1] in their case series. Meallet in 2006 proposed that the use of adjunctive therapies such as mitomycin and beta irradiation also likely compromise the integrity of episcleral conjunctival vessels and underlying tissue, inhibiting adequate wound healing, and leaving the sclera vulnerable to infection.[14] Often corticosteroids given before diagnosis of infective origin have been seen to increase the infection.[1] In our series, 6 cases had a history of steroid

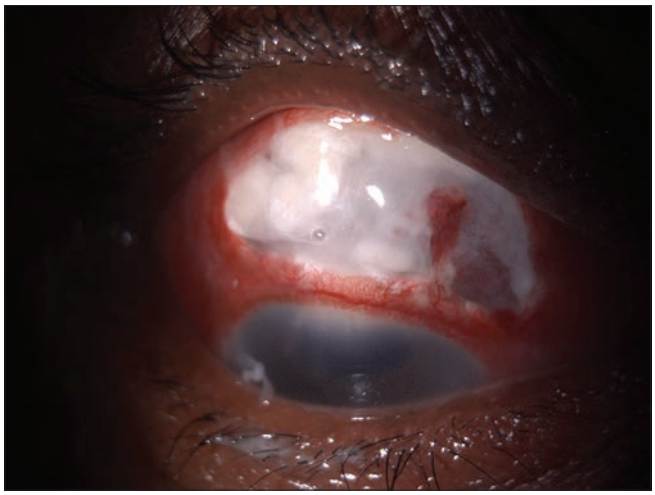


Figure 3: Postcataract surgery scleral wound melt (Case 12)



Figure 4: Mixed fungal and nocardial scleritis postsurgical debridement (Case 1)

use. With no predisposing history of trauma or surgery, immunosuppression due to human immunodeficiency virus or chemotherapy may be a risk factor for spontaneous cases of infectious scleritis.[4,15] There were 4 cases in our series with no predisposing trauma or surgical history. None of the four cases had any endogenous infection or immunosuppression but were under prolonged usage of topical steroids.

P. aeruginosa is reported as the most common causative organism and rarely fungus for infective scleritis.[4,5,16] Infection due to fungus, mostly *Aspergillus*, was found to be most common in our series. In India, fungus is reported to be the most common in many series with *Aspergillus* species being the most common[1,9,11] too. High incidence of fungal infection in India is due to agriculture being the most common occupation among the masses and the tropical hot and humid climatic conditions. Infective scleritis often presents with multifocal nodules, Pseudomonas being most commonly reported with such presentation due to its proteolytic activity leading to intrascleral dissemination.[4-6,9] Another series[1] saw all cases of multifocal presentation due to fungi. Our case series saw multifocal abscess (25%) at presentation in both pseudomonas ($n = 2$) and fungal scleritis ($n = 1$). Some studies have reported.[1,4-6] that multifocal presentation is due to the load of infection and not due to the organism causing it, which can be well correlated to our findings.

As in autoimmune scleritis, patients with infectious scleritis commonly present with redness, pain, and epiphora.[11] Mild-to-moderate pain is generally associated with diffuse and nodular scleritis whereas severe pain is more frequently associated with necrotizing scleritis,[17] suggesting that pain out of proportion to examination findings may indicate underlying possible infectious etiology.[8] Hodson *et al*.[15] reported scleral necrosis (93%) as the most common clinical sign, 67% with adjacent ocular structures such as cornea and extraocular muscle involvement. An anterior chamber reaction >1+ grade is usually present at the initial encounter.[5] In our series, 33% ($n = 4$) had anterior uveitis and 16% ($n = 2$) had corneal infiltrate. Endophthalmitis has also been documented as the presenting finding.[1,6,11,13] Progressive inflammation leads to pupillary membrane, cataract, glaucoma, retinal and choroidal detachment, and endophthalmitis. In our series, 25% cases resolved with cataract, other complications being choroidal detachment ($n = 1$), absolute glaucoma ($n = 1$), and panophthalmitis ($n = 1$).

Pyogenic infection of sclera is difficult to treat because of poor antimicrobial penetration. Abscess exploration with systemic and topical antimicrobial therapy yields superior result.[1,6,18,19] Some studies found that surgical debridement improves visual outcome[20] while some showed that it shortens the course of treatment.[4-6] Pradhan and Jacob[9] showed that chances of globe preservation were better with prompt surgical debridement. Medical therapy was adequate as the sole treatment in only 18% of patients, with most requiring surgical debridement in a large case series studied by Hodson *et al*.[15] A higher rate of enucleation or evisceration was seen in those treated solely with medical methods.[2] Tittler *et al*.[20] showed a 100% globe preservation rate, with fewer complications and shorter hospital stays with prompt surgical debridement at diagnosis (within 2.5 days). We did surgical debridement within a mean duration of 6 days for all our cases expecting a better outcome in terms of globe preservation and were able to achieve the same in 83% of the cases. Scleral patch graft was done in one case (Case 12) in view of large defect postscleral debridement. In addition to surgical debridement and topical and systemic antibiotics, adjunctive procedures such as subconjunctival injections of antibiotic at both ends

of the scleral lesion and wound irrigation with antibiotic solution one to two times a day followed by normal saline after improvement were shown to be beneficial.[6] Meallet[14] could achieve success in treating 6 cases of infective scleritis with the use of continuous subpalpebral lavage antibiotics. In our series, betadine 5% lavage was done in all cases after scleral debridement. Review literature revealed poor outcome in cases of fungal scleritis,[4-6] while 2 studies[9,11] showed good outcome in fungal scleritis with prompt surgical debridement and medical management similar to our study. Useful vision of ≥6/60 was retained in 61% eyes in series by Hsiao *et al*.,[5] 33% by Jain *et al*.,[1] and 83% by Kumar Sahu *et al*.[11] Vision ≥6/60 was retained in 75% of our patients. Seventy one of eyes with presenting visual acuity of >6/60 improved to 6/18 and better. Four out of 18, 3 out of 21, and none out of 17 eyes underwent evisceration in the above studies, respectively. Two out of 12 eyes underwent evisceration in our series. None of our cases showed recurrence once infection resolved completely although 3 cases underwent multiple debridements during active infection. Although the appearance of recurrences after achieving full resolution of scleritis is generally rare,[15,20] still cases should be closely followed up for an extended period of time after resolution.

CONCLUSION

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

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Evaluation of quality of non-mydriatic fundus images obtained with non-contact TrueColor, confocal scanner during third phase of nationwide lockdown

ABSTRACT

Aims: This study aims to evaluate the non-mydriatic fundus image quality obtained with a confocal fundus device. Also, to evaluate the influence of non-mydriatic pupil size on image quality. **Settings and Design:** A cross-sectional study was conducted in the outpatient department of a high-volume tertiary eye care centre in South India during the third phase of the COVID-19 lockdown. **Subjects and Methods:** 831 consenting, consecutive patients (1539 eyes) were photographed from May 5 to May 17, 2020, and were graded excellent, fair, adequate, or inadequate; based on white noise, black noise, and image acquisition signals. Pupil diameters were obtained with light-emitting diode flash technology. **Statistical Analysis:** The collected data were analyzed using SPSS software. Descriptive statistics in the form of frequencies and percentages were calculated. Simple (univariate) linear regression analysis and adjusted regression analysis were used to establish the relationship between pupil size and fundus photo quality. **Results:** The quality of the fundus photo was excellent in 70.12% (n = 1079), fair in 15.72% (n = 242), adequate in 5.78% (n = 89), and inadequate in 8.38% (n = 129). Of the 1410 obtained images (subtracting the inadequate quality images), 87.66% (n = 1236) were normal and 12.34% (n = 174) were pathological. There was a positive linear relationship between pupil size and quality of retinal photograph; OS (R^2 = 0.935) had a slightly better association than OD (R^2 = 0.901). **Conclusions:** The majority of the confocal images were excellent in quality. Our four-point grading system serves as a reliable measure of non-mydriatic photograph quality. Pupil size is a significant predictor of image quality for non-mydriatic photographs in surveillance programs.

Keywords: Confocal fundus scanning, fundus imaging quality, non-mydriatic images, pupil size

INTRODUCTION

The ophthalmic services at our centre resumed from May 5, 2020, when the third phase of the COVID-19 lockdown began in India with considerable relaxations, and continuation of curbs only in containment zones.[1] A coronavirus safety pod; coronicle (corona + cubicle) was created for investigating and examining all outpatient department (OPD) patients [Figure 1].[2] The cubicle was predominantly constructed with transparent acrylic material, and openings were made in front of the chin rest of all ophthalmic gadgets, for the patients to place their chin during testing. In addition, there were inward angulated dents, designed and created for the placement of the patient's legs during investigations and slit-lamp examination, for extra co-operation and comfort.

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While re-starting our ophthalmic outpatient services, there were few challenges [Figure 2] regarding the 90 diopter or 78 diopter examination for the evaluation of fundus; especially the fear of inadvertent patient's face touch or mask touch by the examining doctor, and proximity of examination which can cater to aerosol mediated infection. Also, due to the usage of face shields by the ophthalmologists, the standard stereoscopic examination with 90 diopter or 78 diopter examination was proving very difficult. The similar challenges were encountered with indirect ophthalmoscopy while performing fundus examination. Hence, fundus imaging was done for all; with non-contact, non-mydriatic, automated, confocal, light-emitting diode (LED) fundus capture device (Eidon, iCare) which gave a good 60° exposure of the fundus in a single field with a TrueColor confocal image.

A review of literature has shown that there is improved image quality, enhanced contrast, more finely detailed images, suppression of scattered light, and better imaging of patients with poor dilation with the confocal technology over traditional flash-based systems.[3-9] This area of confocal imaging and its subsequent image quality has been poorly reported in the literature before, especially in Indian settings, as this is a new imaging modality. As the posterior segment examination was done only with the confocal fundus capture device at our centre, during the third phase of COVID-19 nationwide lockdown; and the fundus diagnosis were made only with the images obtained from it, the main aim of this study was to evaluate the quality of non-mydriatic fundus images obtained with this fundus capture device. Our secondary objective was to evaluate the influence of non-mydriatic pupil size on image quality.

SUBJECTS AND METHODS

Population

This is an observational cross-sectional study conducted between May 5 and May 17, 2020, during our emergency ophthalmic outpatient services which was resumed during the third phase of nationwide lockdown during COVID-19 crises. Written, informed consent was obtained from all participants entering the study. There were no specific inclusion or exclusion criteria. All the consenting, consecutive patients presenting to the ophthalmic OPD from May 5 to May 17, 2020 (i.e.,) during the third phase of the nationwide lockdown were included in the study. The idea behind having no exclusion criteria such as lid edema, severe dry eye or wheelchair patient was that we wanted to evaluate the impact of this confocal imaging device as a whole among all the patients presenting to the hospital during that period. Totally 831 consenting, consecutive patients were enrolled in the study during this interval. Subject selection was done from all the patients entering the hospital, not just from a particular department or unit of the hospital. All the patients included in this study were incidentally binocular.

Out of the 831 patients (1662 eyes), 1539 eyes underwent non-mydriatic, non-stereoscopic automated confocal fundus imaging with the Eidon device after a complete ophthalmic examination, including best corrected visual acuity and slit-lamp examination. Based on the nature and progress of disease pathology, certain diseases (such as glaucoma and proliferative diabetic retinopathy [PDR]) which required intervention during the third phase of the lockdown period, were classified as two separate groups, newly diagnosed and already diagnosed/on treatment. 123 eyes were excluded from 1662 eyes due to certain logistic reasons such as shown in Table 1. The study protocol designed followed the tenets of the Declaration of Helsinki.



Figure 1: (a) The Eidon confocal capture device inside the coronicle (corona + cubicle) for examining the fundus, (b) The Coronicle (corona + cubicle)



Figure 2: (a) Ninety diopter fundus examination performed wearing face shield. (b) Inadvertent face-mask touch during 90 diopter examination

Non-mydriatic fundus photograph acquisition and pupil diameter measurement

The photographs were taken between 10 am and 1 pm during the third phase of the nationwide lockdown, in our ophthalmology department set up at the coronicle (corona + cubicle) for OPD patients [Figure 1].[2] The right eye (OD) was imaged first followed by the left eye (OS) after giving a few seconds gap for the pupil to recover. The time gap interval between imaging both eyes (OU) was approximately 15-20 seconds. The time interval set up and movement of the capture machine from OD to OS is an automated process, which is in-built with the machine's technology.

A minimum gap of 3 minutes was then allowed, between two patient examinations at the device, after sanitizing the head and chin rest. The fundus examination was repeated at least two times for one eye. The best photograph with the highest quality for each eye was selected for review, after decision involving two ophthalmologists. The two ophthalmologists were one retina specialist and one glaucoma specialist. They both were Eidon users with experience of more than four years with this technology. Their qualifications were MS in ophthalmology with 2-year fellowship training in their respective sub-specialities. In the case of a tie regarding quality between the two ophthalmologists, the first image of that eye with the highest quality was selected for further analysis. During the process, the image readers were masked from the pupil size to avoid bias.

Non-stereoscopic, non-mydriatic, 60° single field exposure, confocal fundus images of the posterior pole were obtained using the LED capture device (Eidon, iCare).

Table 1: Situations where fundus capture were not performed

Diagnosis	*n* (%)
Acute catarrhal conjunctivitis	65 (52.84)
Foreign body	9 (7.31)
Hordeolum	7 (5.69)
Postoperative inflammation	7 (5.69)
Allergic conjunctivitis	6 (4.87)
Uveitis	5 (4.06)
Bullous keratopathy	4 (3.25)
Severe dry eye	3 (2.43)
Chalazion	3 (2.43)
Traumatic cataract	2 (1.62)
Traumatic iritis	2 (1.62)
Not co-operative (wheelchair patients)	2 (1.62)
Corneal ulcer	1 (0.81)
Blepharitis	1 (0.81)
Congenital cataract	1 (0.81)
Corneal opacity	1 (0.81)
Lid edema	1 (0.81)
Naso-lacrimal duct obstruction	1 (0.81)
Acute dacryocyctitis	1 (0.81)
Total	123 (100)

Images were obtained by a single experienced paramedical practitioner for all patients, under the supervision of an on-site member (corresponding author) of the study team. Photographs were taken in a semi-dark environment created especially for the capture of the non-mydriatic image, to reduce the ambient light exposure preventing constriction of the pupil. Pupil diameters of the patients were also measured with the LED flash technology of the confocal device.

Analysis of the photographs

The 1539 fundus image reviews were done on a 19-inch liquid crystal display monitor (Dell 1907FPV, resolution: 1280 × 1024 for BB; and HP W1907, resolution: 1440 × 900 for CL) using a local area network connection.[2] The photographs were reviewed in the order in which they were obtained. All color images were analyzed exactly as they were outputted from the device. No image processing (e.g., tone and contrast-enhancing/adjustment or color normalization) was performed. The general quality of each ocular fundus photograph was graded on a four-point scale: (1) Excellent, (2) fair, (3) adequate, or (4) inadequate based on illumination, white noise, black noise, and image acquisition signals [Figure 3]. This quality assessment score was created after a focused group discussion with five Eidon ophthalmic users, keeping in mind, common factors influencing imaging such as mentioned above, along with details to major anatomical sites of exposure such as macula and optic disc.

Operational diagnosis-score definition

Excellent scored image

An image was scored as excellent, if white noise or black noise was less than or equal to 25% of the 60° non-mydriatic fundus image area and/or did not involve the optic disc or macula.

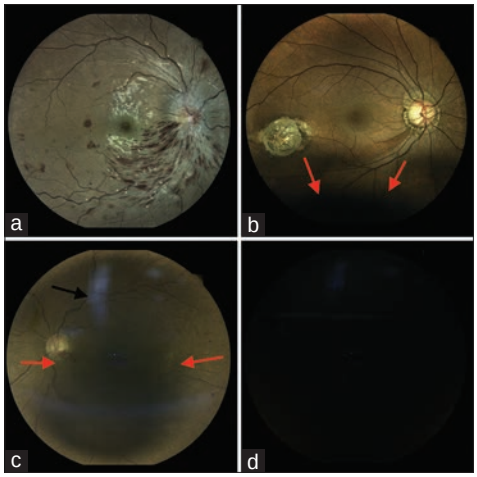


Figure 3: (a) Excellent scored image (No white noise or black noise) (b) Fair scored image with black noise (red arrow) (c) Adequate scored image with black noise (red arrow) and white noise (black arrow) (d) Inadequate scored image with total image showing black noise

Fair scored image

An image was scored as a fair, if the white noise or black noise was between 25% and 75% of the non-mydriatic image area and/or did not involve the optic disc or macula.

Adequate scored image

An image was scored as adequate, if the white noise or black noise was >75% of the non-mydriatic area and/or involve the optic disc or macula but not preventing excluding emergent findings for diagnostic purposes.

Inadequate scored image

An image was scored as inadequate, if the white noise or black noise was 100% throughout the whole non-mydriatic image area, and/or involve the optic disc or macula preventing the exclusion of emergent findings, thus inadequate for diagnostic purposes.

Statistical analysis

The collected data was entered and coded in MS Excel and analyzed using SPSS (Statistical Package for Social Sciences; version 20, IBM USA). Descriptive statistics in the form of frequencies and percentages were then calculated. A Shapiro–Wilk test was performed to assess the normality of distribution. Mann–Whitney U-test and Kruskal-Wallis test (non-parametric test) were utilized for the distribution that did not follow normality. The quality of the images obtained was tested for association with the pupil size. Simple (univariate) linear regression analysis and adjusted regression analysis were used to establish the relationship between fundus photo quality and pupil size. A P value less than 0.05 was considered statistically significant.

RESULTS

Eight hundred and thirty-one consecutive patients (403 males; 428 females) were photographed from May 5 to May 17, 2020. Out of the 1662 eyes (831 patients), a total of 1539 patients' eyes were reviewed after 123 eyes were excluded due to various logistic reasons in whom fundus capture were not performed [Table 1]. The quality of the fundus photo was then evaluated in the remaining 1539 eyes; the quality was excellent in 70.12% (n = 1079), fair in 15.72% (n = 242), adequate in 5.78% (n = 89), and inadequate in 8.38% (n = 129). The reason for inadequate quality was mature cataract in 75.97% (n = 98) and pupil size less than 1.8 mm in 24.03% (n = 31). Out of the 1410 obtained images (excluding the inadequate quality images of 129 images), 87.66% (n = 1236) were normal, and 12.34% (n = 174) were pathological fundus. Out of the 174 pathological eyes, 28.73% (n = 50) were non-PDR (NPDR), 12.07% (n = 21) were previously diagnosed with glaucoma, 10.92% (n = 19) were age-related macular degeneration (ARMD), 9.20% (n = 16) were previously diagnosed with PDR, 6.32% (n = 11) were newly diagnosed with glaucoma, and 4.60% (n = 8) were newly diagnosed with PDR. The mean pupil size was 3.26 ± 0.84 mm in the excellent category, 2.81 ± 1.94 mm in the fair category, and 2.73 ± 0.70 mm in the adequate category [Tables 2 and 3].

Test of normality [Table 4] revealed that the pupil size of adequate quality images in OD male and OD female are the only two groups to follow normality. The pupil size of adequate quality images in OS male and OS female, along with the pupil size of excellent category and fair category images of both sexes separately in OU follows non-normal distribution. When they were evaluated as a whole without gender discrimination, test of normality [Table 5] revealed that the pupil size of adequate quality images in OD follows normality. The pupil size of adequate quality images in OS, along with the pupil size of excellent category and fair category images follows non-normal distribution. Mann–Whitney U-test [Table 6] revealed that there is a significant difference between OD and OS pupil size in the excellent, fair, and overall categories. As the pupil size of adequate quality images category in OD follows normality and the pupil size of adequate quality images category in OS follows non-normality, the above Mann–Whitney U-test cannot be performed between them.

Descriptive analysis of the pupil size with age and gender is shown in Table 7. Evaluating the pupil size with age and gender using Kruskal–Wallis test [Table 8] revealed that there is a significant difference between OD pupil size, OS pupil size, and OU pupil size (together) when compared with age. Whereas, there was no significant difference between OD pupil size, OS pupil size, and OU pupil size (together) when compared with gender.

There was a positive linear relationship between the pupil size and quality of retinal photograph; OS (R^2 = 0.935) had a slightly better linear relationship than OD (R^2 = 0.901). Model summary of adjusted regression analysis of the pupil size OU with age and gender is shown in Table 9. Coefficients of adjusted regression analysis of the pupil size OU with age and gender depicted [Table 10] that, if age decreased then the pupil size increased and it was statistically significant (beta coefficient −0.064, P = 0.04); and females had slightly larger pupil size compared to male, but was not statistically significant (beta coefficient 0.043, P = 0.052). Table 11 depicts the model fitness information (multinomial logistic regression) of image quality with the pupil size that was assessed using the Chi-square test. The table showed that there was a significant relationship between the image quality and the pupil size. Table 12 depicts the Pseudo

Table 2: Sex, age and pupil size distribution of the study population

	n (mean±SD)		
	Male	**Female**	**Total**
Number of patients, *n* (%)	342 (48.51)	363 (51.49)	705 (100)
Age (mean±SD)	47.19±21.04	46.45±18.96	46.81±19.99
Mean pupil size OD	342 (3.3±0.81)	363 (3.48±1.59)	705 (3.39±2.88)
Mean pupil size OS	342 (2.82±0.71)	363 (2.93±0.86)	705 (2.88±0.79)
Mean pupil size OD - Excellent category	292 (3.46±0.76)	326 (3.61±0.86)	618 (3.54±0.82)
Mean pupil size OS - Excellent category	217 (2.90±0.69)	244 (3.03±0.81)	461 (3.97±0.76)
Mean pupil size OD - Fair category	55 (2.88±0.73)	43 (3.50±0.4)	98 (3.13±0.63)
Mean pupil size OS - Fair category	83 (2.52±0.65)	61 (2.42±0.54)	144 (2.48±0.61)
Mean pupil size OD - Adequate category	13 (2.89±0.79)	17 (2.73±0.62)	30 (2.79±0.70)
Mean pupil size OS - Adequate category	24 (2.65±0.68)	35 (2.70±0.71)	59 (2.68±0.70)

SD - Standard deviation, OD - Right eye, OS - Left eye

Table 3: Pupil size distribution for different quality of images in both eyes

	n (mean±SD)		
	Pupil size - Excellent category	**Pupil size - Fair category**	**Pupil size -Adequate category**
All the participants	1079 (3.26±0.84)	242 (2.81±1.94)	89 (2.73±0.70)
OD	618 (3.54±0.82)	98 (3.13±0.63)	30 (2.79±0.71)
OS	461 (2.97±0.76)	144 (2.48±0.61)	59 (2.68±0.70)

OD - Right eye, OS - Left eye, SD - Standard deviation

Table 4: Test of normality revealed that the pupil size of adequate quality images in right eye male and left eye female were the only two groups to follow normality

	Shapiro-Wilk		
	Statistic	**df**	**Significance**
Age			
Male	0.963	342	0.000
Female	0.967	363	0.000
Pupil size OD			
Male	0.974	342	0.000
Female	0.446	363	0.000
Pupil size OS			
Male	0.942	342	0.000
Female	0.933	363	0.000
Pupil size categories of OD male			
Excellent	0.978	292	0.001
Fair	0.919	55	0.001
Adequate	0.911	13	0.059
Pupil size categories of OS male			
Excellent	0.952	217	0.000
Fair	0.872	83	0.000
Adequate	0.878	24	0.014
Pupil size categories of OD female			
Excellent	0.980	326	0.001
Fair	0.265	43	0.000
Adequate	0.905	17	0.057
Pupil size categories of OS female			
Excellent	0.943	244	0.000
Fair	0.894	61	0.001
Adequate	0.870	35	0.001

The pupil size of adequate quality images in OS male and OS female, along with the pupil size of excellent category and fair category images of both sexes separately in OU followed non-normal distribution. OS - Left eye, OU - Both eyes, OD - Right eye

R-Square (multinomial logistic regression) of image quality with the pupil size. The model accounted for 3.4%–6.2% of the variance and represented relatively decent-sized effects. Table 13 depicts the likelihood ratio test (multinomial logistic regression) of image quality with the pupil size. This proved that the independent variables such as OD pupil size and OS pupil size of the patients were significant. Table 14 depicts the parameter estimates (multinomial logistic regression) of image quality with the pupil size. From Table 14, in that instance, SPSS was treating the "excellent category" images as the referent group. A one-unit increase in the variable (OD pupil size) was associated with a 0.019 increase in the relative log odds of being in fair image quality versus overall image quality; which was not statistically significant. A one-unit increase in the variable (OS pupil size) was associated with a 0.258 decrease in the relative log odds of being in fair image quality versus overall image quality; which was statistically significant. A one-unit increase in the variable (OD pupil size) was associated with a 0.787 decrease in the relative log odds of being in adequate image quality versus overall image quality, which was statistically significant. A one-unit increase in the variable (OS pupil size) was associated with a 0.472 increase in the relative log odds of being in fair image quality versus overall image quality, which was statistically significant.

DISCUSSION

The rationale for the choice of this particular instrumentation

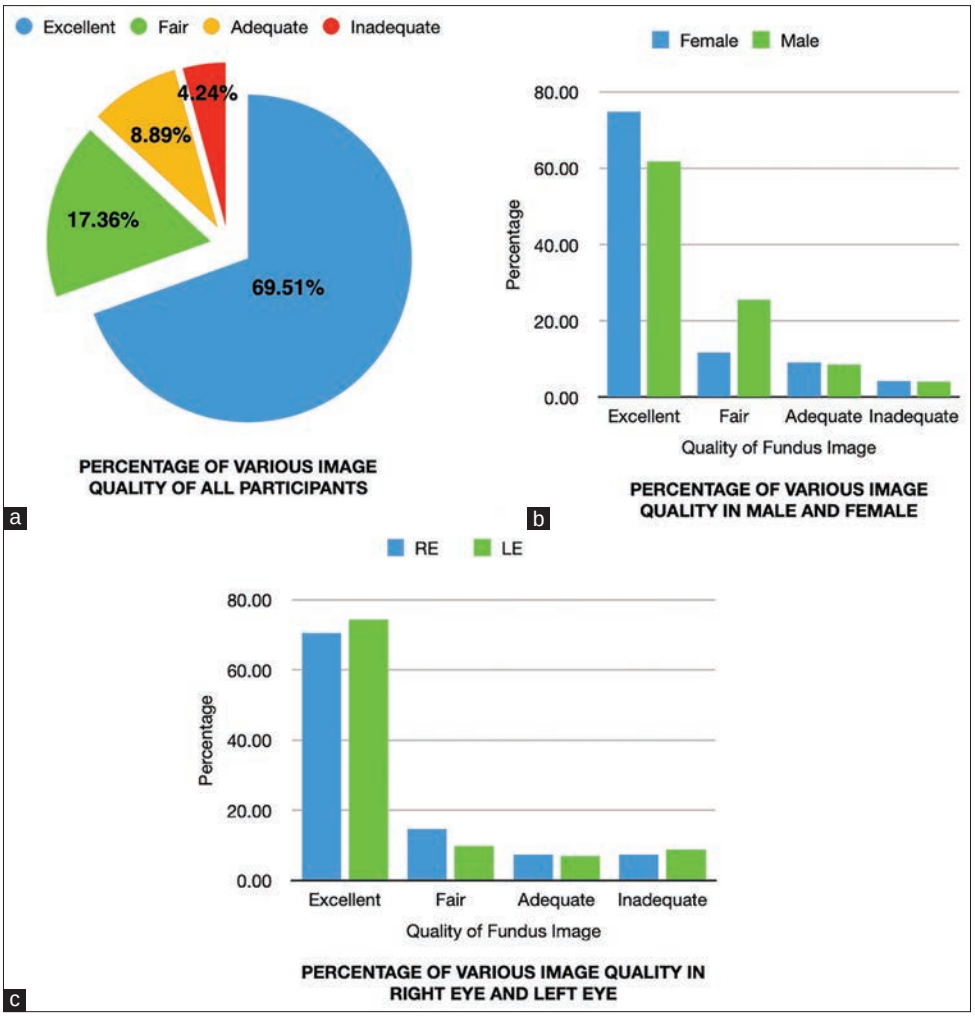


Figure 4: (a) Percentage of various quality of images of all participants. (b) Percentage of various quality of images in male and female. (c) Percentage of various quality of images in right eye and left eye

Table 5: Test of normality revealed that the pupil size of adequate quality images in right eye follows normality

	Categories	Shapiro-Wilk		
		Statistic	df	Significance
Pupil size OD	Excellent (OD)	0.980	618	0.000
Pupil size OS	Excellent (OS)	0.980	461	0.000
Pupil size OD	Fair (OD)	0.256	98	0.000
Pupil size OS	Fair (OS)	0.881	144	0.000
Pupil size OD	Adequate (OD)	0.932	30	0.051
Pupil size OS	Adequate (OS)	0.883	59	0.000

The pupil size of adequate quality images in OS, along with the pupil size of excellent category and fair category images in OU follows non-normal distribution. OS - Left eye, OU - Both eyes, OD - Right eye

in this study for retinal imaging was that; it is a non-contact modality which is fully automated and does not require any skill from the examiner, who is performing the test, thus eliminating the human interface during performing the test; which is ironically the need during the pandemic. Another perceived advantage of this fundus capture device was its quick acquisition time of less than 1 min, for both eyes cumulatively, which in-turn reduces patient waiting time inside the hospital premises, during this COVID-19 crises. This instrument is, otherwise also regularly present at the study institute and all the authors were experienced with the usage and interpretation of the TrueColor confocal images obtained with them.

TrueColor confocal imaging - evolution

Color fundus photography is an important tool in the diagnosis and monitoring of various retinal pathologies. Clear and detailed photographs allow an accurate evaluation of the ocular fundus and provide precise documentation of the retinal findings; that can be archived or shared for telemedicine applications as well, or be used as a valuable educational tool.[3] In digital fundus cameras, a bright flash is used to illuminate the ocular fundus; and the light reflected is then captured on the pixel array of a charge-coupled device, thus subsequently generating a digital image. Conventional fundus cameras illuminate large areas of the retina, typically

Table 6: Mann-Whitney U-test revealed that there was a significant difference between right eye and left eye pupil size in the excellent, fair and overall categories

Pupil size	Excellent	Fair	Overall categories
Mann-Whitney U	101905.500	3954.500	149405.000
Wilcoxon W	286136.500	12461.500	421614.00
Z	−10.381	−4.620	−10.888
Asymptotic significance (two-tailed)	0.000	0.000	0.000

As the pupil size of adequate quality images category in OD follows normality and the pupil size of adequate quality images category in OS follows non-normality, the above Mann-Whitney U-test cannot be performed between them. OD - Right eye, OS - Left eye

Table 7: Descriptive analysis of the pupil size with age and gender

	n	Mean rank
Age		
OD		
Below 17	51	484.34
17-41	193	456.88
Above 41	461	317.00
Total	705	
OS		
Below 17	51	485.43
17-41	193	434.62
Above 41	461	326.10
Total	705	
OU		
Below 17	102	955.19
17-41	386	878.25
Above 41	922	649.69
Total	1410	
Gender		
OD		
Male	342	358.66
Female	363	377.52
Total	705	
OS		
Male	342	357.53
Female	363	378.55
Total	705	
OU		
Male	705	717.33
Female	705	754.08
Total	1410	

OS - Left eye, OU - Both eyes, OD - Right eye

with a flash lamp, and capture 35°-45° field of view, and provide high-resolution digital images. Currently, color images acquired with traditional fundus cameras play a pivotal role in the documentation, diagnosis, and monitoring of retinal disorders.[4,5] However, conventional flash devices frequently capture color images that are oversaturated in the red channel and are washed out in the green and blue channels, yielding a retinal picture that often looks flat and reddish.[6]

The Eidon device is a slit confocal system that captures 60°, 14-megapixel retinal images in an automated fashion through a non-mydriatic pupil (as small as 1.8 mm). The light source is a broad spectrum white-light LED with a wavelength of 440–650 nm. Sharp, high contrast, and TrueColor image of the retina are obtained. The color of the Eidon images are more balanced (i.e., not saturated by the red component) and "richer" (i.e. greater color discrimination and broader gamut) compared with those obtained with a traditional flash color fundus camera; thus yielding greater discriminative power and diagnostic accuracy, providing accurate documentation of the appearance of retina.[10]

Rationale for nil exclusion criteria

The idea behind having no exclusion criteria such as media opacities, pupil size less than 1.8 mm, lid edema, severe dry eye or wheelchair patient were that; we wanted to evaluate the impact of this technology as a whole, among all the patients presenting to the hospital, during the third phase of the nationwide lockdown. Although the association of the lockdown, with the use of this instrument, is a pragmatic reality; if such a situation arises in the future (such as second wave of pandemic as happening currently), then users would benefit from the data of patients, for whom fundus examination was not performed on a statistical scale due to various reasons listed in the manuscript [Table 1]. On the hindsight, if exclusion criteria were used and these conditions had been removed, then the statistical data of these patients would fall in our blind spot.

Quality of images

Out of the 1662 eyes (831 patients), a total of 1539 patient's eyes were reviewed after 123 eyes were excluded in whom fundus capture were not performed [Table 1]. The quality of fundus photo [Figure 4] was excellent in 70.12% (n = 1079), fair in 15.72% (n = 242), adequate in 5.78% (n = 89), and inadequate in 8.38% (n = 129). The majority of the images were excellent in quality. The reason is as follows: confocal systems allow the capture of reflected light through a small confocal aperture, which suppresses any scattered or reflected light outside the focal plane that could potentially blur the image. This results in a sharp, high-contrast image of an object layer located within the focal plane.[11] The rate of occurrence of low-quality images has been reported at

3.7%–19.7% in clinical studies.[12] In our study, the percentage of poor (inadequate quality) images was 8.38%. The reason for inadequate quality was mature cataract in 75.97% ($n = 98$) and pupil size <1.8 mm in 24.03% ($n = 31$). Due to the phase 1 and phase 2 lockdown, we experienced a surge in mature cataract OPD patients, once we resumed eye care services. And in all mature cataracts, fundus imaging was not possible resulting in inadequate image quality. Similarly, when the pupil size was <1.8 mm, the white light LED was not able to generate fundus images due to a very small confocal aperture.[11]

Pathological fundus

Out of the 1410 obtained fundus images (after excluding the 129 inadequate quality images), 174 images were pathological. Out of the 174 pathological eyes, we were able to pick up and diagnose many new cases, which warranted immediate intervention. The pathological fundi list diagnosed is shown in Table 15. Diseases such as NPDR, glaucomatous optic disc damage, PDR, ARMD, and retinitis pigmentosa were commonly diagnosed. Relatively, rare entities such as retinoschisis were also diagnosed. Pathological retina was identified, dilated and a mosaic view revealing up to the equator were imaged, and treated accordingly.

Pupil size and image quality

Incidentally, it was found that the pupil size had a major role in influencing the quality of the fundus images [Figure 5]. The mean pupil size was 3.26 ± 0.84 mm in the excellent category, 2.81 ± 1.94 mm in the fair category, and 2.73 ± 0.70 mm in the adequate category [Table 3]. When separately studied, the OD mean pupil size was 3.54 ± 0.82 mm, 3.13 ± 0.63 mm, and 2.79 ± 0.71 mm, respectively and the OS mean pupil size was 2.97 ± 0.76 mm, 2.48 ± 0.61 mm, 2.68 ± 0.70 mm, respectively. There was a positive association between the pupil size and quality of retinal photograph in both eyes; OS (R2 = 0.935) had a slightly better association than OD (R2= 0.901). The mild disparity between eyes (OS > OD) was likely due to a greater flash exposure in OS, as OD was studied first followed by OS.

R-Squared (R^2 or the coefficient of determination) is a statistical measure in a regression model that determines the proportion of variance in the dependent variable, that can be explained by the independent variable. The R^2 shows how well the data fit the regression model (the goodness of fit). However, it does not provide information about a causal relationship between the independent and dependent variables. In addition, it does not indicate the correctness of the regression model. Therefore, conclusions about the model were drawn in this study by analyzing R^2 together with other variables in a statistical model. The regression analysis allows to predict an outcome, which can be a good quality image or a poor quality image as seen in this study based on unit changes in the pupil size.

Table 8: Evaluating the pupil size with age and gender using Kruskal - Wallis test revealed that there was a significant difference between right eye pupil size, left eye pupil size and both eyes pupil size (together) when compared with age

	OD	OS	OU
Age			
χ^2	80.447	56.741	116.357
df	2	2	2
Asymptotic significance	0.000	0.000	0.000
Gender			
χ^2	1.446	1.801	2.752
df	1	1	1
Asymptotic significance	0.229	0.180	0.097

Whereas there was no significant difference between OD pupil size, OS pupil size and OU pupil size (together) when compared with gender. OS - Left eye, OU - Both eyes, OD - Right eye

Table 9: Model summary of adjusted regression analysis of the pupil size both eyes with age and gender

R	R^2	Adjusted R^2	SE of the estimate
0.078	0.006	0.005	1.6821

SE - Standard error

Table 10: Coefficients of adjusted regression analysis of the pupil size both eyes with age and gender depicted that if age decreased, then the pupil size increased and it was statistically significant (beta coefficient=−0.064, P=0.04); and females had slightly larger pupil size as compared to males and it was not statistically significant (beta coefficient 0.043, P=0.052)

Pupil size	β	Significant
Constant		0.000
Age	−0.064	0.004
Sex	0.043	0.052

Table 11: Depicts the model fitness information (multinomial logistic regression) of image quality with the pupil size, which was assessed using the Chi-square test

Model	Model fitting criteria−2 log likelihood	Likelihood ratio tests		
		χ^2	df	Significant
Intercept only	794.456			
Final	759.405	35.051	4	0.000

There was a significant relationship between the image quality and the pupil size

Table 12: Depicts the pseudo R^2 (multinomial logistic regression) of image quality with the pupil size

Pseudo R2	Pseudo R2 Value
Cox and Snell	0.047
Nagelkerke	0.062
McFadden	0.034

The model accounted for 3.4%-6.2% of the variance and represented relatively decent-sized effects

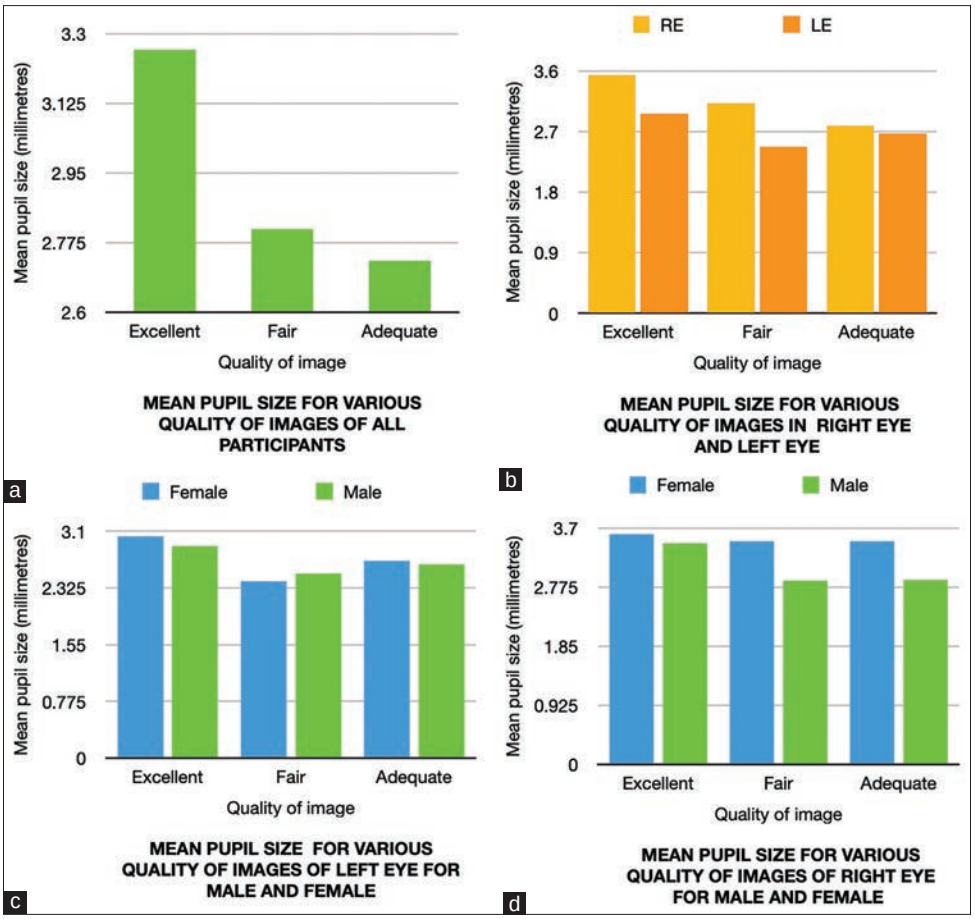


Figure 5: (a) Mean pupil size for various quality of images of all participants. (b) Mean pupil size for various quality of images of right eye and left eye. (c) Mean pupil size for various quality of images of left eye for male and female. (d) Mean pupil size for various quality of images of right eye for male and female

Table 13: Depicts the likelihood ratio test (multinomial logistic regression) of image quality with the pupil size

Effect	Model fitting criteria−2 log likelihood of reduced model	Likelihood ratio tests		
		χ^2	df	Significant
Intercept	786.414	27.009	2	0.000
OD pupil size	784.905	25.500	2	0.000
OS pupil size	772.914	13.509	2	0.001

This proved that the independent variables such as OD pupil size and OS pupil size of the patients were statistically significant. OD - Right eye, OS - Left eye

Table 14: Depicts the parameter estimates (multinomial logistic regression) of image quality with the pupil size

Overall image quality	*B*	df	Significant	Exp (*B*)	95% CI for Exp (*B*) (lower bound-upper bound)
Fair					
Intercept	−1.040	1	0.000		
OD pupil size	0.019	1	0.798	1.019	0.882-1.178
OS pupil size	−0.258	1	0.017	0.772	0.625-0.955
Adequate					
Intercept	−1.148	1	0.000		
OD pupil size	−0.787	1	0.000	0.455	0.330-0.628
OS pupil size	0.472	1	0.010	1.603	1.122-2.291

In this instance, SPSS was treating the excellent as the referent group. A one-unit increase in the variable (OD pupil size) was associated with a 0.019 increase in the relative log odds of being in fair image quality versus overall image quality; which was not statistically significant. A one-unit increase in the variable (OS pupil size) was associated with a 0.258 decrease in the relative log odds of being in fair image quality versus overall image quality; which was statistically significant. A one-unit increase in the variable (OD pupil size) was associated with a 0.787 decrease in the relative log odds of being in adequate image quality versus overall image quality, which was statistically significant. A one-unit increase in the variable (OS pupil size) was associated with a 0.472 increase in the relative log odds of being in fair image quality versus overall image quality, which was statistically significant. OD - Right eye, OS - Left eye, CI - Confidence interval, SPSS - Statistical package for social sciences

Table 15: 174 pathological fundi diagnosed with Eidon fundus capture device

Various fundus pathologies	*n* (%)
Nonproliferative diabetic retinopathy	50 (28.73)
Glaucoma on Rx	21 (12.06)
Age related macular degeneration	19 (10.91)
Post PRP - proliferative diabetic retinopathy	16 (9.19)
Newly diagnosed glaucoma	11 (6.32)
Proliferative diabetic retinopathy (newly diagnosed)	8 (4.59)
Retinitis pigmentosa	8 (4.59)
Vitreous hemorrhage	5 (2.87)
Macular hole	4 (2.29)
Glaucoma suspect	4 (2.29)
Tractional retinal detachment	4 (2.29)
Mixed retinopathy	4 (2.29)
Branched retinal vein occlusion	3 (1.72)
Epiretinal membrane	3 (1.72)
Juxta-foveal telangiectesia	2 (1.14)
Normal tension glaucoma with splinter haemorrhage	2 (1.14)
Retinoschisis	2 (1.14)
Central serous chorioretinopathy	1 (0.57)
Clinically significant macular oedema	1 (0.57)
Neovascular glaucoma	1 (0.57)
Cystoid macular oedema	1 (0.57)
Retinal detachment	1 (0.57)
Subhyaloid haemorrhage	1 (0.57)
Postretinal detachment surgery	1 (0.57)
Chorioretinal scar	1 (0.57)
Total	174 (100)

PRP - Panretinal photocoagulation

A review of comparison with similar market and post-market studies

Many market and post-market studies have been performed and inferred that confocal imaging has an excellent standard of fundus image quality. Additionally, Eidon TrueColor confocal technology applied with wide-field imaging is particularly crucial as it helps to improve the detection, analysis, and monitoring of pathologies that could arise in the periphery of the retina. EIDON's wide-field features help to preserve the sharpness and details even in the periphery, facilitating improved and early diagnosis.[10] Although the analysis of fundus photography utilizing non-mydriatic fundus camera has been studied in several studies across the globe, no study has so far reported the image quality analysis with confocal fundus camera.[13-17]

A positive correlation between pupil size and quality of fundus photo was noted in a study by Sangave *et al*.[18] Along with it, they noted a correlation disparity between eyes, which was attributed to greater flash exposure in OS, similar to our study. In non-mydriatic photography, it is reported that there is a faster pupil recovery time with lower flash intensities, thus improving image quality in the fellow eye.[15] In previously conducted studies, the percentage of ungradable images was found to be between 4% and 34%.[19] In our study, the inadequate ungradable images were minimal (about 8%) which falls within the category.

Our study has found a negative correlation between age and pupil size stating that, as age increases pupil size decreases. Higgs *et al.* suggested the same in an indirect way, stating that as age increases the percentage of ungradable fundus photo taken through non-mydriatic fundus camera increases, which corresponds to the decreasing pupil size with age.[20] A comparison between a white LED confocal imaging system and a conventional flash fundus camera using chromaticity analysis revealed that Eidon provides more balanced color images, with a wider richness of color content, compared to a conventional flash fundus camera. The overall higher chromaticity of Eidon may provide benefits in terms of discriminative power and diagnostic accuracy.[10]

Limitations

1. Confocal image quality may reduce in cases with pupil size less than 1.8 mm
2. Cost of this instrumentation is very high and may not be feasible for all ophthalmic centres
3. The two image readers were not masked of the findings from one another. The intra-observer and inter-observer agreement between the image quality between the two readers was not assessed.

Suggestions

1. Pupil diameters of all the patients were measured with the LED flash technology of the confocal device. To the best of our knowledge, this is the first study to measure pupil diameter with LED technology. Further studies are needed to throw more light on the potential of LED flash technology, for pupil size measurements
2. To draw a definitive conclusion on the clinical utility of this new confocal device, a prospective comparative study comparing the performance of human graders and artificial intelligence-based algorithms of this device with conventional device fundus cameras are warranted.

CONCLUSIONS

This study demonstrated that the new confocal, white-light LED system, Eidon, produces good quality color images, providing accurate documentation of retinal appearance and diagnosis. This new fundus imaging system has the potential to enhance patient care, especially in high-volume centres, as the total examination time is only one minute cumulatively for both eyes together, thus indirectly reducing waiting time inside hospital premises, minimizing hospital-acquired infection during the pandemic.[21,22,23]

Our four-point grading system serves as a reliable measuring tool for evaluating the quality of non-mydriatic fundus photographs. Pupil size is a significant predictor of image quality for non-mydriatic fundus photographs in high-volume tertiary eye care surveillance programs.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

A comparative study of efficacy and safety of alcaftadine 0.25% versus olopatadine hydrochloride 0.2% in allergic conjunctivitis at a tertiary care hospital

ABSTRACT

Background: Ocular itching is the hallmark symptom of allergic conjunctivitis, accompanied by tearing, conjunctival redness, eyelid swelling, and chemosis. Alcaftadine and olopatadine hydrochloride are classified as dual-acting antiallergic agents, used in the treatment of allergic conjunctivitis. **Objective:** The aim is to compare the efficacy and safety of alcaftadine 0.25% and olopatadine hydrochloride 0.2% eye drops among patients with allergic conjunctivitis. **Settings and Design:** Ophthalmology outpatient department at Minto Ophthalmic Hospital, Bangalore Medical College and Research Institute, Bengaluru; prospective, randomized, comparative study. **Subjects and Methods:** This study was conducted among 120 patients suffering from grade 3 Allergic conjunctivitis and efficacy measured in terms of proportion of patients achieving symptomatic relief of allergic ocular signs and symptoms from grade 3 to grade 0 from baseline to 2 weeks, using Total Ocular Symptoms Score (TOSS) and Conjunctival Hyperemia scale. Safety assessed by monitoring treatment-emergent adverse effects. Continuous data assessed by unpaired, paired *t*-test and repeated measures-ANOVA and categorical data by Chi-square test. $P < 0.05$ was considered statistically significant, whereas < 0.001 as highly significant. **Results:** Greater proportion of patients achieved symptomatic relief in the Alcaftadine group (98.3%) compared to the olopatadine hydrochloride group (90%) at end of 2 weeks. A significant and faster reduction in TOSS score was observed from baseline to 2 weeks in alcaftadine treated group compared to the olopatadine hydrochloride group ($P < 0.05$). Adverse events reported were headache, burning sensation, and mild redness in both groups. **Conclusion:** Alcaftadine 0.25% demonstrated greater efficacy in reducing ocular signs and symptoms of allergic conjunctivitis from baseline to 2 weeks, compared to olopatadine hydrochloride 0.2% with minimal side-effects.

Keywords: Alcaftadine 0.25% eye drops, allergic conjunctivitis, conjunctival hyperemia scale, olopatadine hydrochloride 0.2% eye drops, total ocular symptoms score

INTRODUCTION

Allergic conjunctivitis affects 40% of the global population. Activation of H1, H2 histamine receptors leads to ocular itching and vasodilatation, respectively.[1-4] Olopatadine hydrochloride is a selective H1-receptor antagonist; mast-cell stabilizer with additional anti-inflammatory effects,[5] whereas alcaftadine, a dual-acting agent (anti-histaminic, mast-cell stabilizer with anti-inflammatory property), provides relief from ocular itching by inverse agonistic effects on H1, H2, and H4 receptors.[6,7] Considering the paucity of comparative studies, with regard to efficacy and safety among Indian

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patients, this study was undertaken. The objective was to compare the reduction in ocular signs and symptoms using the Total Ocular Symptoms Score (TOSS).

SUBJECTS AND METHODS

It is a prospective, randomized, comparative study conducted from May 2019 to December 2019, after obtaining Institutional Ethics Committee approval and written informed consent, patients of either sex aged 18–40 years, diagnosed with allergic conjunctivitis with grade 1–3 ocular allergic symptoms were included in the study.[8] Patients not willing for written informed consent, patients with grade 4 severity of ocular allergic symptoms, patients with known hypersensitivity to the study medications or their components (including benzalkonium chloride), intraocular pressure of more than 21 mm Hg in either eye or any type of glaucoma, those on other medications which may interfere with the study like decongestants, prostaglandin derivatives, ocular or systemic nonsteroidal anti-inflammatory drugs and corticosteroids, those having active ocular infection or serious ocular pathological condition, a history of dry eye syndrome, patients who have undergone ocular surgical interventions within the past 3 months, female patients who are pregnant or lactating or considering pregnancy, psychiatric or emotional disturbance in patients which would limit the ability of the patients to comply were excluded.

A total of 120 patients suffering from allergic conjunctivitis were recruited after fulfilling the inclusion and exclusion criteria, allotted into two groups of 60 each and randomized in 1: 1 ratio, to receive either alcaftadine 0.25% eye drops, 1 drop once daily or olopatadine hydrochloride 0.2% eye drops, 1 drop once daily for 14 days. Demographic data, ocular and medical histories, concomitant medications, physical examination, clinical examination including recording of vital signs, ophthalmological examination, and details of drug prescription by the treating Ophthalmologist were recorded in the study pro forma at the baseline visit (visit 1). Follow-up visits were on day 3 (visit 2), day 7 (visit 3) and day 14 (visit 4) after administering the study drugs. A deviation of ± 1 day for the first follow-up and ± 2 days for subsequent follow-up were accepted. At each follow-up visit, data on concomitant medications, ocular symptoms (graded by the patients) and ocular signs (graded by slit-lamp examination by the investigator) and adverse events (AEs) were collected. In case of relapse, the patient was asked to visit OPD on Day 21.

Ocular symptoms and signs were recorded from baseline (Day 1) and adverse effects if any were recorded on follow-up visits (Day 3, 7, 14). The primary efficacy outcome measure was the proportion of patients achieving symptomatic relief of allergic ocular symptoms from grade 3 to grade 0 from baseline to 2 weeks using TOSS score and conjunctival hyperemia as shown in Table 1 (represents grading of ocular signs and symptoms)[8] and Table 2 (represents the scale of the assessment of conjunctival hyperemia),[9] respectively, and the secondary outcome was the number and severity of AEs on the follow-up visits.

Sample size calculation:

Sample size is calculated using the formula:

$$N = \frac{(r+1)\left(Z_{\alpha/2} + Z_{1-\beta}\right)^2 P(1-P)}{(P_1 - P_2)^2}$$

$n1$ and $n2$ = sample size for Group 1 and Group 2

such that, $N = n1 = n2$

ratio $r = n1/n2 = 1/1 = 1$

$Z\alpha$ = normal deviate at a level of significance = 1.96 for 5% level of significance

$Z_{1-\beta}$ = normal deviate at 1-β +% power = 0.84 at 80% power

p_1 = prevalence in group 1 = 0.76 [6]

p_2 = prevalence in group 2 = 0.5

$p_1 - p_2$ = Difference in proportion of events in two groups = 0.26[6]

P = Pooled prevalence = $(p_1 + p_2)/2 = 0.63$

$$N = \frac{(1+1)(1.96+0.84)^2 (0.63)(0.37)}{(0.26)^2} = 54$$

Considering 10% drop out rate,

$$N1 = \frac{N}{1-q}$$

$N1$ = Total sample size including drop outs

N = Total sample size

q = anticipated drop outs = 0.1 (10%)

$$N1 = \frac{54}{1-0.1} \approx 60$$

A sample size of 120 was taken for better validation of results.

Statistical analysis

The data collected were analyzed statistically using descriptive statistics, namely mean, standard deviation and

Table 1: Grading of ocular signs and symptoms[8]

Symptoms	Grade 1	Grade 2	Grade 3	Grade 4
Itching	Mild	Occasional	Frequently	Continuous
Watering	Absent	Occasional	Frequently	Continuous
Photophobia	Absent	Mild grade	Moderate grade (unable to open eye in intense light)	Severe grade (unable to open eye in normal light)
Lid edema and chemosis	Absent	Absent	Only mild oedema	Oedema with chemosis
Conjunctival hyperemia	Mild congestion	Pinkish discoloration of conjunctiva	Reddish discoloration of conjunctiva	Bright red conjunctiva

Table 2: Scale of assessment of conjunctival hyperemia[9]

Description	Hyperemia degree	Right eye	Left eye
Normal	No	0	0
Inconsistent rose red hyperaemia	Trace	0.5	0.5
Reddish colour	Mild	1	1
Bright red colour	Moderate	2	2
Bright and intense diffuse hyperaemia	Severe	3	3

proportion/percentage wherever applicable. Continuous data were assessed by the Unpaired *t*-test used between the two groups and RM-ANOVA within the group and categorical data were assessed using Chi-square test using VassarStats statistical computation. $P < 0.05$ was considered statistically significant, whereas < 0.001 was highly significant.

RESULTS

120 patients diagnosed with allergic conjunctivitis with grade 3 ocular allergic symptoms who met inclusion criteria were enrolled in the study. Table 3 represents the baseline demographic profile of the patients included in the study. There was no statistical difference in age and gender in both the groups ($P = 1.00$; $P = 0.74$, respectively). Both the treatment groups were matched with respect to baseline demographic characteristics.

Patients with a mean age of 27.9 ± 7.7 years in alcaftadine group and 26.7 ± 5.38 years in olopatadine group. There were 39 (65%) male and 21 (35%) female in alcaftadine group and 35 (58.3%) male and 25 (41.7%) female patients in the olopatadine group.

Efficacy parameters

The ocular symptoms and signs assessed using TOSS score were itching (100%), tearing (83.3%), redness (71.6%), and swelling (19%) of the conjunctiva.

Figure 1 shows the TOSS score from visit 1 (baseline) to visit 4 in both groups. Table 4 and Figure 2 represent the number of patients with their Total Ocular Symptom Score at different visits from baseline visit 1 (Day 1) to visit 4 (Day 14).

Both the groups showed a significant improvement in TOSS scores from baseline to 14 days. The total ocular symptom score showed consistent decrease in subsequent visits in both the study groups and it was statistically significant from baseline to 14th day ($P = 0.03$). Table 5 shows the TOSS score at different visits.

Conjunctival Hyperemia grading from baseline to day 14 is represented in Table 6 and Figure 3. Conjunctival hyperemia was significantly reduced in both the treatment groups. There is no statistical significance between the groups while assessing the conjunctival hyperemia scale in all the visits.

Within the individual group of alcaftadine 0.25% [Table 7] and olopatadine hydrochloride 0.2% [Table 8], the TOSS score and conjunctival hyperemia scale were statistically highly significant ($P < 0.001$) from baseline to follow-up visit 4. The number of patients in alcaftadine group who achieved faster symptomatic relief were higher, compared to olopatadine hydrochloride 0.2% group.

SAFETY PARAMETER

Adverse drug reactions (ADRs) encountered in our study were headache, burning sensation, dizziness, and mild redness in the conjunctiva. All four ADRs were mild, self-limiting and did not require the discontinuation of therapy. Table 9 represents the ADRs in both groups.

DISCUSSION

The conjunctiva of the eye is continually exposed to a variety of airborne antigens that can lead to inflammation, often termed allergic conjunctivitis. Allergic conjunctivitis is an ocular surface inflammatory disease that is predominantly IgE-mediated Type I hypersensitivity reaction where allergen binds to specific IgE molecules, triggers mast cell degranulation and subsequent increase in histamine release leading to activation of both H1 and H2 types of histamine receptors leading to ocular itching and vasodilatation associated with ocular redness, eyelid swelling, and chemosis, respectively.

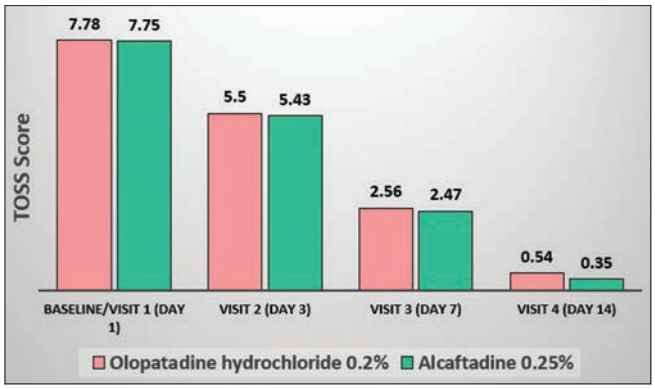


Figure 1: TOSS Score from visit 1 (baseline) to visit 4 in both the groups

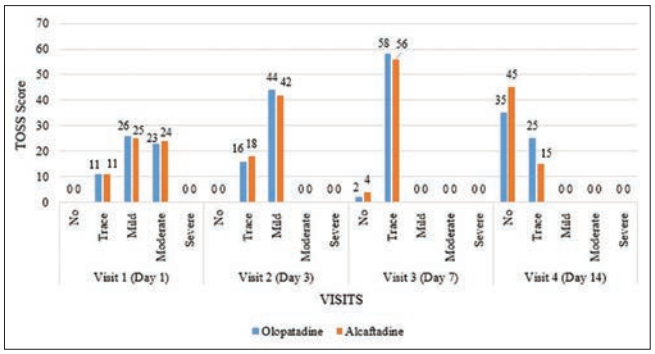


Figure 2: Total Ocular Symptom Score at different visits

Pharmacological treatment of allergic conjunctivitis includes H1 receptor blockage, mast cell stabilization, and blocking of cytokine production and prostaglandin formation. Topical antihistamines are first-line agents in the treatment of allergic conjunctivitis. Currently, alcaftadine 0.25% and olopatadine hydrochloride 0.2% are the only approved once-daily, dual-acting anti-allergic agents for allergic conjunctivitis which includes inhibition of histamine receptor activation directly and reduction of allergic responses by stabilizing mast cells indirectly.[6,10]

Olopatadine hydrochloride is a selective histamine H1-receptor antagonist and mast-cell stabilizer with additional anti-inflammatory effects such as suppression of interleukins 6 and 8 production by inhibiting histamine-related signaling pathways.[6] Alcaftadine is an anti-allergic agent that provides relief from ocular itching by inverse agonistic effects on H1, H2 and H4 histamine receptors in the early phase and also stabilizes mast cells by inhibiting the release of mediators such as cytokines and lipid mediators in the late phase of ocular allergic response in allergic conjunctivitis. Furthermore, it decreases chemotaxis and inhibits eosinophil activation and thereby exerts anti-inflammatory properties.[6,11]

In the present study, the mean age was comparable and matched in both groups. The majority of patients enrolled in our study were 26.7 ± 5.38 years in olopatadine group and 27.9 ± 7.7 years in alcaftadine group. There were 35 (58.3%) male and 25 (41.7%) female patients in the olopatadine group and 39 (65%) males and 21 (35%) females in alcaftadine group, suggesting a slight male preponderance, that was also observed in a study by Nakatani *et al*.,[9] which could be due to the socioeconomic status of the patients visiting our Government hospital and the social set up where the majority of the females do not report to the hospital.

The present study was conducted to compare the efficacy and safety of dual-acting, once daily, topical antihistamine

Table 3: Baseline demographic characteristics (60 patients in each group)

	Alcaftadine 0.25%	Olopatadine hydrochloride 0.2%	*P*
Age (years), mean±SD	27.9±7.7	26.7±5.38	1.00
Gender			
Males	39	35	0.74
Females	21	25	

P<0.05 is considered statistically significant. SD – Standard deviation

Table 4: Number of patients with their total ocular symptoms score from baseline visit 1 to visit 4

Visits	TOSS score	*n*	Trace	Mild	Moderate	Severe
Visit 1 (day 1)	Olopatadine	0	11	26	23	0
	Alcaftadine	0	11	25	24	0
Visit 2 (day 3)	Olopatadine	0	16	44	0	0
	Alcaftadine	0	18	42	0	0
Visit 3 (day 7)	Olopatadine	0	2	58	0	0
	Alcaftadine	0	4	56	0	0
Visit 4 (day 14)	Olopatadine	35	25	0	0	0
	Alcaftadine	45	15	0	0	0

TOSS – Total ocular symptoms score

solutions, alcaftadine 0.25% versus olopatadine hydrochloride 0.2% eye drops in the treatment of allergic conjunctivitis. Our findings of the study showed greater reduction in TOSS (Total Ocular Symptom Score) from baseline to 2 weeks in alcaftadine group compared to olopatadine hydrochloride group (statistically significant, $P < 0.05^{*}$). Similarly, the conjunctival hyperemia scale also showed larger reduction within the group of alcaftadine and olopatadine treated patients ($P < 0.001$) from baseline (Day 1) to follow-up visit (Day 14).

The study confirmed the treatment outcome differences between alcaftadine 0.25% and olopatadine hydrochloride 0.2% eye drops. Alcaftadine 0.25% treated group achieved faster symptomatic relief of allergic ocular symptoms from grade 3 to grade 0, using TOSS score at visit 2 (Day 3) and visit 3 (Day 7) than olopatadine hydrochloride 0.2% group. There was a significant reduction in ocular symptoms and signs at

the end of the study (Day 14/visit 4) in the alcaftadine group than olopatadine hydrochloride group. The common adverse effects in both groups were headache, burning sensation, and mild redness.

A study by Meena and Gupta,[8] showed that alcaftadine 0.25% ophthalmic solution provided greater symptomatic relief of ocular itching postadministration with a similar safety profile, compared to olopatadine hydrochloride 0.2%. It also mentioned that there were significantly lower mean ocular itch scores in alcaftadine 0.25% treated patients than olopatadine hydrochloride 0.2% group at the 2nd and 3rd follow-ups. The study also confirmed the difference in treatment outcomes between alcaftadine 0.25% and olopatadine 0.2% in preventing signs and symptoms of allergic conjunctivitis on day 3 and day 7 of post-treatment instillation. In the present study, alcaftadine 0.25% showed a statistically significant reduction in TOSS score on Day 14 (visit 4), compared to olopatadine group.

A study by Greiner *et al.*[11] showed that alcaftadine 0.25% and olopatadine 0.2% had significantly lower mean scores of ocular itching and conjunctival redness compared to placebo at visits 3 and 4. Furthermore, alcaftadine 0.25% was found to be effective and superior over placebo, by reducing ocular symptoms and signs at 15 min and 16 h post instillation suggesting the rapid onset of action and substantial duration of action. Headache was one of the AEs observed in the present study was similar to the study by Greiner *et al.*[11]

A study by Singh *et al.* mentioned that Alcaftadine showed marginal superiority in efficacy of reducing ocular itching and conjunctival redness score and found equally safe when compared to olopatadine group.[12]

A study by Nakatani *et al.*,[9] revealed that alcaftadine 0.25% dosed 8 h before allergen challenge was found to be effective or superior in preventing ocular signs and symptoms of Japanese cedar pollen-induced allergic conjunctivitis, compared to olopatadine 0.2% ophthalmic solution (challenged 4 h postdose). The results of the study showed statistical significance in reduction of ocular itching score and conjunctival hyperemia scale in alcaftadine 0.25% group compared to olopatadine 0.2% group. Furthermore, the age and gender of patients enrolled in our study were similar to the study by Nakatani *et al.*

Table 5: Total ocular symptom score at different visits

Visits	Alcaftadine 0.25%	Olopatadine hydrochloride 0.2%	*P*
Baseline/visit 1 (day 1)	7.75±0.6	7.78±0.59	0.93
Visit 2 (day 3)	5.43±0.41	5.5±0.4	0.91
Visit 3 (day 7)	2.47±0.26	2.56±0.23	0.57
Visit 4 (day 14)	0.35±0.11	0.54±0.14	0.03*

*$P<0.05$ is considered statistically significant

Table 6: Conjunctival Hyperemia Scale from visit 1 (baseline) to visit 4 in both the groups

Visits	Alcaftadine 0.25%	Olopatadine hydrochloride 0.2%	*P*
Baseline/visit 1 (day 1)	1.38±0.22	1.4±0.23	0.92
Visit 2 (day 3)	0.85±0.156	0.87±0.157	0.88
Visit 3 (day 7)	0.35±0.072	0.37±0.073	0.63
Visit 4 (day 14)	0.008±0.0167	0.05±0.039	0.05

$P<0.05$ is considered statistically significant

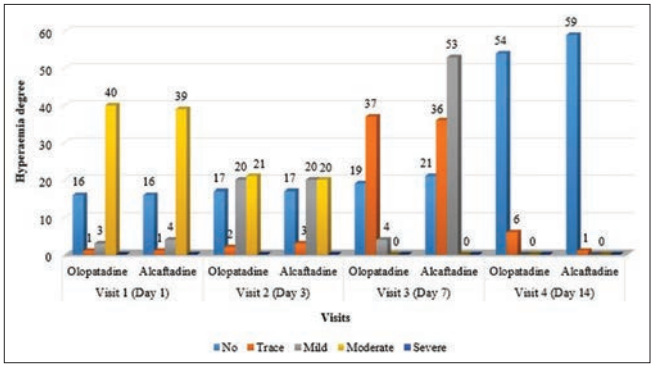


Figure 3: Conjunctival hyperemia grading from baseline (Day 1) to visit-4 (Day 14)

Table 7: Total ocular symptoms score and Conjunctival Hyperemia Scale (within alcaftadine 0.25% group)

Assessment	Visit 1 (day 1)	Visit 2 (day 3)	Visit 3 (day 7)	Visit 4 (day 14)	*P*
TOSS score	7.75±0.6	5.43±0.41	2.47±0.26	0.35±0.11	<0.001*
Conjunctival Hyperaemia Scale	1.38±0.22	0.85±0.15	0.35±0.072	0.008±0.0167	<0.001*

*$P<0.001$ is considered as highly significant. TOSS – Total ocular symptoms score

Table 8: Total ocular symptoms score and Conjunctival Hyperemia Scale (within olopatadine hydrochloride 0.2% group)

Assessment	Visit 1 (day 1)	Visit 2 (day 3)	Visit 3 (day 7)	Visit 4 (day 14)	*P*
TOSS score	7.78±0.59	5.5±0.4	2.56±0.23	0.54±0.14	<0.001*
Conjunctival Hyperemia Scale	1.4±0.23	0.87±0.157	0.37±0.073	0.05±0.039	<0.001*

*$P<0.001$ is considered as highly significant. TOSS – Total ocular symptoms score

Table 9: Adverse drug reactions in both the groups

Adverse drug reaction	Olopatadine 2%	Alcaftadine 2.5%	*P*
Headache	2	1	0.35
Burning sensation	3	1	
Dizziness	0	2	
Mild redness	1	1	

P<0.05 is considered statistically significant

A study by Ackerman *et al*.,[13] showed differences in relief of itch between alcaftadine 0.25% and olopatadine 0.2% ophthalmic solutions, at the earliest time point measured postconjunctival allergen challenge (CAC) (3 min) and effective in preventing ocular itching at 16-and 24-h postinstillation in a CAC. Furthermore, it stated that alcaftadine group was only active treatment that provided statistical significance in relief of chemosis post 24 h instillation.[3] The current study showed patients achieved faster relief of itching, redness, tearing and chemosis of the conjunctiva at day 14 (follow-up visit 4) more in the alcaftadine group compared to the olopatadine hydrochloride group.

In pooled analysis of two multicenter, randomized clinical trials, done by McLaurin *et al*.,[6] revealed that alcaftadine and olopatadine hydrochloride was superior to placebo at relieving ocular itching alcaftadine 0.25% ophthalmic solution provided greater relief at 16 h postadministration and significantly lower mean itch score at 3 min post CAC with similar safety profile, compared to olopatadine hydrochloride 0.2%

A study on the conjunctival epithelium and eosinophil recruitment in a murine model with allergic conjunctivitis by Ono and Lane,[10] mentioned that alcaftadine significantly inhibited eosinophil recruitment by a broad spectrum of H1, H2, and H4 histamine receptors antagonism and have a protective effect on epithelial tight junction protein expression in the conjunctiva, compared to olopatadine hydrochloride treated group. It also demonstrated the ability to protect epithelial tight junction protein markers from allergic inflammation-based degradation, whereas olopatadine failed to protect from degradation ZO-1 junctional protein.[9]

The present study shows that alcaftadine 0.25% is superior in efficacy and safety when compared to olopatadine hydrochloride 0.2% in the treatment of allergic conjunctivitis. This is a prospective, randomized study design and the use of standard validated tools such as TOSS score and conjunctival hyperemia scale for assessing the efficacy of treatments has added strength to the study.

The study was limited by its relatively smaller sample size. Therefore, further studies with larger sample size are required to evaluate the efficacy and safety of alcaftadine 0.25% versus olopatadine 0.2% in the treatment of allergic conjunctivitis.

CONCLUSION

In allergic conjunctivitis, both alcaftadine 0.25% and olopatadine hydrochloride 0.2% were found effective in relieving ocular signs and symptoms, but alcaftadine 0.25% was found to be superior in terms of efficacy, compared to olopatadine hydrochloride 0.2% with minimal side-effects.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

To study the effect of intravitreal ozurdex implant in cases of retinal vein occlusion

ABSTRACT

Introduction: Retinal vein obstruction is one of the leading causes of severe vision impairment and blindness with treatment options mainly including laser, vascular endothelial growth factors, and steroids. This study investigates an intravitreal dexamethasone implant (ozurdex), its efficacy, and complications in patients of retinal venous occlusion. **Methods:** A prospective, interventional study involving 30 patients with retinal venous occlusion. Patients diagnosed with RVO who had vision loss of at least two lines on Snellen's chart and increased central macular thickness (CMT) on OCT were included in the study. All the parameters such as best-corrected visual acuity (BCVA), CMT, and intraocular pressure (IOP) were noted at baseline for the affected eye. The patients were followed up at 1 month, 2 months, and 3 months following the implant. **Result:** Baseline parameters were comparable between the groups. Eyes receiving the implant had a statistically significant improvement ($P < 0.001$) in BCVA on the Snellen chart over the 3 months. There was also a constant decrease in macular edema and the mean difference value of CMT between baseline and 1 month, 2 months, and 3months were also found to be statistically significant. Also, a comparison of IOP between two-time points was done, between baseline and 1 month, 2 months, 3 months, and the mean difference value in IOP was also found to be significant but clinically well within the normal physiological range. **Conclusion:** The study concluded that an intravitreal dexamethasone implant is an effective treatment for retinal venous occlusion, and it has a statistically significant and clinically meaningful effect on BCVA and CMT. However, it may be associated with a significant rise in IOP but it is well within the physiological range.

Keywords: Dexamethasone implant, intravitreal dexamethasone, intravitreal implant, ozurdex, retinal venous occlusion

INTRODUCTION

Retinal vein obstruction is one of the leading causes of severe vision impairment and blindness. It is the most common retinal disorder after diabetic retinopathy and age related macular degeneration (ARMD).[1] Among retinal vein occlusion branches, the retinal vein is most common followed by central retinal vein occlusion. The prevalence of BRVO is estimated to be between 0.6% and 1.1% and that of central retinal vein occlusion (CRVO) to be between 0.1% and 0.4%.[2,3]

Various local and systemic factors play a part in the pathophysiology of retinal vein occlusion. Occlusion of the central retinal vein leads to the backup of the blood in the retinal venous system and increased resistance to venous blood flow. This increased resistance causes stagnation of the blood and ischemic damage to the retina.[4] It has been postulated that ischaemic damage to the retina stimulates increased production of vascular endothelial growth factor (VEGF) in the vitreous cavity.[5] Increased levels of VEGF cause capillary leakage leading to macular edema and may also stimulate neovascularization of the posterior and anterior segments.[6]

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Currently, there are no proven treatment options available, so management has the two-fold aim of managing modifiable risk factors and treating complications like macular edema and neovascularization. The most common treatment involves periodic injections into the eye of an anti-VEGF drug to reduce the new blood vessel growth and swelling. Anti-VEGF drugs include bevacizumab, ranibizumab, and aflibercept. Intravitreal steroids have also been studied and used to treat macular edema associated with retinal venous occlusion.[7-9] They reduce inflammatory mediators through a more widespread action that blocks VEGFs, inflammatory cytokines, and prostaglandins. Currently, the response is positive but limited due to side effects.

Ozurdex (FDA approved for diabetic macular edema in November 2015) is dexamethasone eluting vitreous implant which contains 0.7 mg (700 mcg) of dexamethasone in the NOVADUR solid polymer sustained-release drug delivery system. It is released in a biphasic manner over 6 months, with higher concentrations released for the first 6 weeks, followed by lower concentrations for the following months. After this time, the implant dissolves to CO2 and H2O leaving no residue in the eye. We, therefore, studied the effect of intravitreal dexamethasone implant on best-corrected visual acuity (BCVA), central macular edema, and intraocular pressure (IOP).

METHODS

The study was designed as a prospective, longitudinal, interventional analytic study. It was conducted at the department of ophthalmology of a tertiary health care institute and included a total of 30 patients. This work was carried out according to the guidelines of the institutional review board and ethical clearance was taken. Written informed consent with full disclosure was obtained from the patients before participation in the study.

Patients diagnosed with retinal vein occlusion who had vision loss of at least two lines on the Snellen chart and increased central macular thickness (CMT) on OCT were included in the study. Exclusion criteria included patients having high IOP/glaucoma, significant cataract changes, diabetic retinopathy, ARMD, and refractive error of more than 5D. At the time of enrolment in the study, a complete medical and ocular history was taken. Comprehensive ophthalmic examination, including BCVA, gonioscopy, a detailed slit-lamp examination and fundus examination with +90D lens, Optical Coherence Tomography (CIRRUS HD-OCT Model 500) to document macular edema in the form of CMT, and IOP by Non-contact Tonometer (SHIN-NIPPON NCT-200) was recorded in all patients. Fundus fluorescein angiography was used to evaluate the extent of vascular occlusion and the degree of ischemia.

On the day of the procedure, the patient's eye was dilated well and topical lignocaine 4% was instilled. A distance of 3.5 mm was marked from the limbus in the inferotemporal or inferonasal quadrant. Prefilled ozurdex implant was injected with a 22-gauge needle in an L-shaped fashion, bevel up first going parallel to the limbus for 1 mm into the sclera and then turning the needle and entering the vitreous cavity through the pars plana aiming toward the posterior pole. A click sound confirms the delivery of the implant. The needle was then withdrawn along the same path.

All the above parameters were noted at baseline for the involved eye. The patients were followed-up at 1 month, 2 months, and 3 months following the implant into the vitreous cavity, and all the parameters were recorded for the involved eye at each visit. We also examined all the eyes with the implant on the day of the procedure or a day after the procedure to rule out any acute complications like IOP spike or vitreous hemorrhage.

RESULTS

The mean age of patients in our study was 60.93 ± 13.07 years. There were 19 males (63.3%) and 11 females (36.7%). Out of 30 patients, 40% had CRVO, 36.7% had SuperoTempoarl - Branch retinal vein occlusion, and the remaining 23.3% had InferoTemporal - Branch retinal vein occlusion. The right eye was affected in 17 (56.7%) patients, whereas the left eye in 13 (43.3%) patients.

Visual acuity

At baseline, BCVA was <6/60 in 6 (20%) patients, 6/60 in 8 (26.7%), 6/36 in 9 (30%), 6/24 in 6 (20%), 6/18 in 1 (3.3%), and no patients had vision 6/12 or better. At 1 month, 1 (3.3%) patient improved to 6/12, 8 (26.7%) had 6/18, 13 (43.3%) had 6/24, 3 (10.0%) had 6/36, 2 (6.7%) had 6/60, and only 3 (10.0%) patients still had BCVA <6/60. At 2 months, all patients had vision 6/60 or better; 1 (3.3%) patient improved to 6/9, 4 (13.8%) had 6/12, 13 (44.8%) had 6/18, 4 (13.8%) had 6/24, 3 (10.3%) had 3/36, and remaining 4 (13.8%) patients had vision 6/60. One patient was lost to follow-up.

At 3 months, 2 (6.9%) patients now had 6/9, 2 (10.3%) had 6/12, 8 (27.6%) had 6/18, 11 (37.9%) had 6/24, 1 (3.4%) had 3/36, and remaining 4 (13.8%) patients still had vision 6/60. Thus, the eyes receiving the implant had a highly significant improvement ($P < 0.001$) in BCVA over 3 months.

CMT

The mean value of CMT at baseline, 1, 2, and 3 months were 411.48 μ ± 83.97, 356.62 μ ± 60.61, 319.86 μ ± 47.11, and 295.34∝ ± 46.76, respectively, with statistically

significant difference ($P < 0.001$) [Figure 1]. A post hoc comparison of CMT between two-time points was done. Between baseline and 1st month, 2nd month, and 3rd month, mean difference value in CMT was found to be 54.862 µ, 91.621 µ, 116.138 µ, respectively, and they were found to be significant ($P < 0.001$). The mean difference valued of CMT between 1 month and 2 months, 1 month and 3 months, 2 months and 3 months were 36.759 µ, 61.276 µ, 24.517 µ, respectively, and these were also found to be statistically significant [Figure 2].

IOP

The mean values of IOP at baseline, 1, 2, and 3 months were 15.72 mmHg ± 1.62, 18.59 mmHg ± 2.18, 18.00 mmHg ± 1.75, and 17.52 mmHg ± 1.46, respectively [Figure 3]. Post implant comparison of IOP between two time-points was done. Between baseline and 1st month, 2nd months, and 3rd months, the mean difference value in IOP was found to be − 2.862 mmHg, −2.276 mmHg, −1.793 mmHg ($P < 0.001$) which are significant but clinically well within the normal physiological range. The mean

CMT	N	Mean ± SD	p value
Baseline	29	411.48 ± 83.97	<0.001
1 month	29	356.62 ± 60.61	
2 months	29	319.86 ± 47.11	
3 months	29	295.34 ± 46.76	

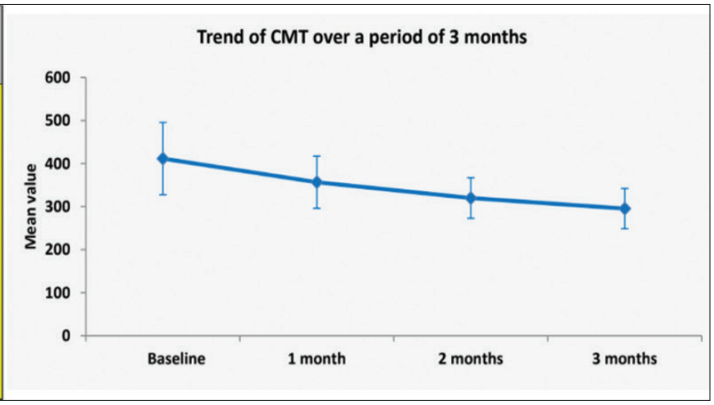


Figure 1: Trend of central macula thickness (CMT) over a period of 3 months

CMT		Mean Difference	Std. Error	p value	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
At Baseline	1 month	54.862*	5.822	<0.001	38.334	71.39
	2 months	91.621*	8.478	<0.001	67.552	115.689
	3 months	116.138*	10.448	<0.001	86.478	145.798
1 month	2 months	36.759*	4.074	<0.001	25.193	48.325
	3 months	61.276*	6.655	<0.001	42.382	80.17
2 months	3 months	24.517*	3.398	<0.001	14.871	34.164

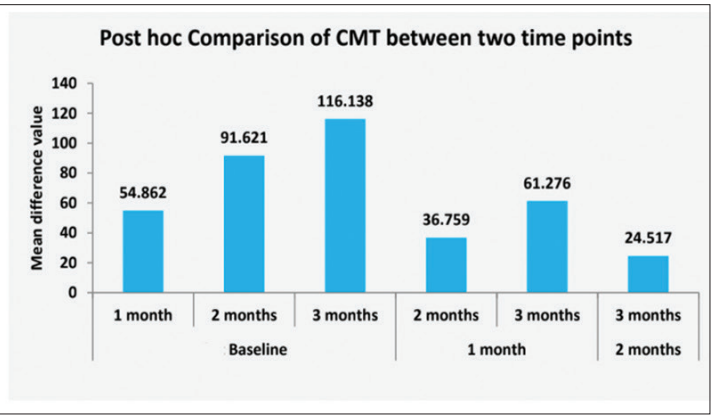


Figure 2: Post Hoc comparison of central macular thickness (CMT) between two time-points

IOP	N	Mean ± SD	p value
Baseline	29	15.72 ± 1.62	<0.001
1 month	29	18.59 ± 2.18	
2 months	29	18.00 ± 1.75	
3 months	29	17.52 ± 1.46	

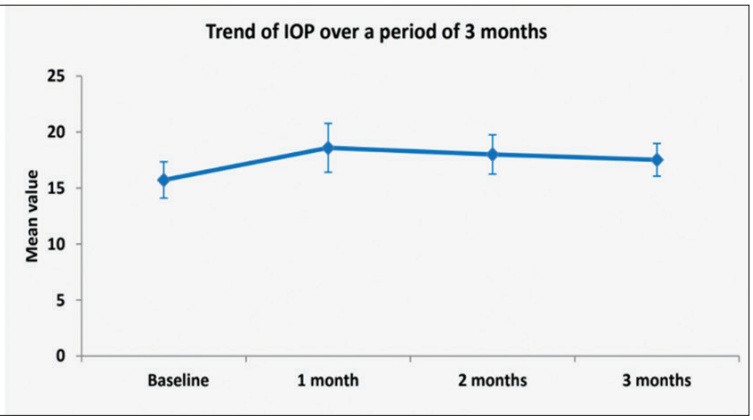


Figure 3: Trend of intraocular pressure (IOP) over a period of 3 months

difference value in IOP between 1 month and 2 months is 0.586 mmHg ($P = 0.384$), 1 month and 3rd month is 1.069 mmHg ($P = 0.037$), between 2nd month and 3rd month is 0.483 mmHg ($P = 0.538$), which are not significant [Figure 4].

DISCUSSION

Macular edema is a frequent manifestation of retinal venous occlusion and is a common cause of the diminution of vision. Intravitreal administration of corticosteroids reduces capillary permeability and the formation of secondary macular edema of various etiologies.[10] They also restrict the migration of leukocytes and inhibit the formation of VEGF factor, prostaglandins, and other pro-inflammatory cytokines.[11] When administered directly into the vitreous body, we can achieve the appropriate concentration of the drug directly at the site of the disease, decreasing the systemic side effects, and thus the route of administration also plays an important role.[12]

Studies have shown clinically significant improvement and increased vision after the administration of the dexamethasone implant in patients with RVO. In the present study, the status of visual acuity, CMT, IOP after 0.7 mg dexamethasone (ozurdex) implant in cases of both CRVO and BRVO were analyzed in 30 patients, and a significant improvement was observed between pre- and post-injection CMT and BCVA values ($P < 0.001$) in both groups.

In our study, the change in mean visual acuity from baseline to 1 month, 2 months, and 3 months were found to be statistically significant ($P < 0.001$). Similarly, the studies performed by Joshi L *et al*.[13] and Haller JA *et al*.[14] also showed significant improvement of BCVA after dexamethasone 0.7 mg (ozurdex) implant. The Geneva study results showed visual improvement in the early period after injection, its effect showed a peak at 6 weeks and lasted for a max of 3 to 4 months, after which BCVA decreased.[14] As our study was followed-up for 3 months, further effects could not be evaluated.

The mean difference value of CMT between baseline and 1st, 2nd and 3rd month was found to be 54.862 µ, 91.621 µ, 116.138 µ, respectively, and all the values were found to be statistically significant. Moreover, a decrease in CMT between 1 month to 2nd and from 2nd month to 3rd month were also found to be statistically significant. The studies conducted by Xioxin Li Ningli *et al*.[15] also showed statistically significant change in CMT post intravitreal dexamethasone implant injection.

On assessing adverse effects of the implant, our study showed the mean difference value in IOP from baseline and monthly follow-ups were statistically significant but were within the physiological range. Also, the mean change from 1 month to 2nd and 3rd month was not significant. The study conducted by Mayer WJ *et al*.[16] showed statistically significant IOP elevation post intravitreal dexamethasone 0.7 mg implant. However, the study conducted by Haller JA *et al*.[14] showed that IOP peaked at day 60 (16%) but was no different from sham by day 180.

Many studies have shown clinically significant improvement and increased vision after the administration of the intravitreal dexamethasone injection in patients with RVO.[17,18] The Geneva study showed the efficacy of dexamethasone implant as 1st line treatment for RVO-related macular edema and included 40 patients with non-ischemic BRVO and 31 with CRVO. It showed significant improvement in both BCVA and CMT. However, more than 50% recurrence rates were seen in both groups after 1st and 2nd injection.[14] Similarly, Joshi *et al*.[13] reported recurrence rates of 56% and 60% in

IOP		Mean Difference	Std. Error	p value	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
At Baseline	1 month	-2.862*	0.288	<0.001	-3.68	-2.044
	2 months	-2.276*	0.333	<0.001	-3.22	-1.332
	3 months	-1.793*	0.303	<0.001	-2.655	-0.932
1 month	2 months	0.586	0.304	0.384	-0.277	1.449
	3 months	1.069*	0.361	0.037	0.044	2.094
2 months	3 months	0.483	0.275	0.538	-0.297	1.262

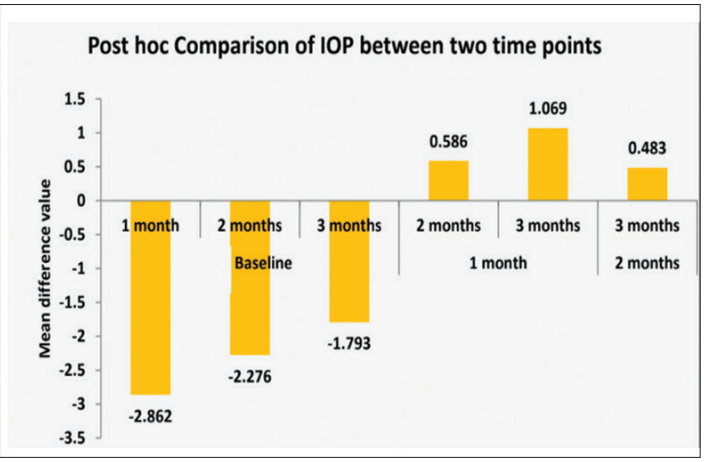


Figure 4: Post Hoc comparison of intraocular pressure (IOP) between two time-points

patients with RVO after the first and the second Ozurdex injections, respectively.

Many studies like Chiquet *et al*.[19] compared the efficacy of intravitreal dexamethasone injection and anti-VEGF therapies in patients with treatment-naive RVO-related macular edema. They concluded that anti-VEGF-administered PRN monthly and intravitreal dexamethasone injection PRN at 6-month intervals yielded comparable outcomes after 12 months follow-up. Other studies like Coscas *et al*.[20] have reported good efficacy and safety profiles of repeated dexamethasone injections.

Our study shows that ozurdex implant (dexamethasone 0.7 mg) significantly improves visual acuity and CMT in patients of retinal vein occlusion (CRVO and BRVO). The study has some limitations such as a small sample size and short duration follow-up, but it was comparable to earlier studies. It may be associated with a significant rise in IOP, but this increased IOP can be medically managed. Rarely, there may be a chance of endophthalmitis which should be promptly diagnosed and managed.

Within the last decade, intravitreal pharmacotherapy has revolutionized the therapeutic options for macular edema (ME)-associated retinal vascular diseases. With both anti-VEGF agents and corticosteroids, substantial visual and morphological improvement has been achieved as compared to those that are solely treated using laser therapy in the treatment of BRVO and CRVO. Our study also shows that ozurdex is an effective and safe method for first-line management of retinal vein occlusion. Moreover, compared with anti-VEGF therapies, the burden of injections is also reduced. Safety concerns associated with the use of ozurdex include a transient increase in IOP that is usually amenable to medical management and the formation or progression of cataracts.

Thus, dexamethasone implant is assuming increasing popularity due to its good potency and dose-consistency, the prolonged duration of action, and, compared to other corticosteroids, its favorable safety profile. However, further longer duration and bigger sample size studies are required. Alternative treatment modalities such as anti-VEGF injections and laser treatment should be available for patients who do not achieve visual improvement with ozurdex and vice versa.

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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Original Article

Efficacy, feasibility, and patient acceptance of using low-dose atropine in retarding myopia progression: A general ophthalmologist's perspective

ABSTRACT

Purpose: Assessing efficacy of atropine 0.01% eye drops in retarding myopia progression in children, the feasibility of its use, and patient acceptance outside institutional practice. **Design:** Prospective observational hospital-based study was conducted in children who were prescribed aropine 0.01% eye drops to retard the progression of myopia. **Methods:** Fifty-seven children who showed a documented progression of 0.5 diopters (D) of myopia were prescribed atropine 0.01% eyedrops. In those patients who followed up, the mean change in spherical equivalent was assessed using a paired *t*-test and a pairwise correlation test. Data of those who were lost to follow-up were evaluated. **Results:** Out of the 57 children 10 opted out of the study and of the remaining 47 children 20 (42.55%) were lost to follow-up. The mean age of the remaining 27 children was 9.04 ± 3.05 years and 48.1% (n = 13) were female. The mean age of dropouts was significantly higher than those who were followed up (P = 0.003). The mean duration of follow-up was 10.8 ± 5.1 months (range 3–23 months). The mean spherical equivalent from baseline to last follow-up was 0.329 by the paired sample *t*-test (P < 0.001). Twelve (44.4%) of the 27 children showed a progression of myopia despite treatment. **Conclusion:** Mean change in spherical equivalent in our study is comparable to previous studies with hardly any adverse effects suggesting efficacy of atropine 0.01%; practical hurdles in follow-up and adherence need to be improved with better patient education.

Keywords: Atropine, Myopia, Acceptance

INTRODUCTION

Myopia is a major public health problem with a higher risk for several ocular complications that may lead to irreversible blindness. High myopia that is defined by the World Health Organization as −5 diopters (D) or greater is associated with degenerative changes in the macula, optic nerve, and peripheral retina and potentially blinding complications such as retinal detachments, myopic choroidal neovascularization, myopic macular degeneration, foveoschisis, glaucoma, and cataract.[1-3] An estimated 2%–5% of Caucasian populations and 5%–10% of Asian populations have high myopia and an estimated 1% of Caucasian populations and 1%–3% of Asian populations have pathologic myopia.[4-6] The estimate of high myopia is expected to increase from 2.7% in 2000 to 9.8% in 2050 while the overall prevalence of myopia will increase from 22.9% in 2000 to 49.7% in 2050.[6] The prevalence of myopia in school-going children in India was reported as 13.1% with a mean myopic spherical error of −1.86 ± 1.4 diopters which shows that myopia is a significant health problem in our country.[7]

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It is not considered a major problem despite these staggering numbers as it is viewed as a refractive error that can be managed with spectacles, contact lenses, or refractive surgery. Myopia progresses at about −1 D per year in East Asians and around −0.5 D per year in Caucasians.[8,9] Atropine is the only medication that has shown consistent effectiveness to reduce the progression of myopia.[10,11] Higher concentrations of atropine such as 1% or 0.5% are effective in retarding myopia progression but have rates of photophobia as high as 100% and dropout rates ranging from 16% to 58%.[12,13] The efficacy of atropine eye drops in varying concentrations from 0.5% to 0.01% has been demonstrated in the atropine for the treatment of myopia (ATOM) 1 and ATOM 2 studies.[14] Lower concentrations of atropine (0.05%, 0.01%, and 0.025%) have also been found to be effective in arresting the progression of myopia in the LAMP study.[15] A multicentric trial from India has shown promising results in reducing myopia progression in mild-to-moderate myopia.[16] However, the systemic and ocular side effects of atropine can affect long-term use and lead to a high dropout rate, especially with higher concentrations. Thirty-four (17%) of participants who withdrew from the ATOM 1 study stated hypersensitivity, glare, and poor near-visual acuity as the reasons for withdrawal, and 4.1% of children in 0.1% and 0.5% atropine group reported allergic conjunctivitis in the ATOM 2 study.[14] We designed a prospective observational study of a group of children with myopia who were prescribed 0.01% atropine at a private eye hospital in north Kerala with a specific aim to understand the uptake and compliance with the prescribed dose of atropine for myopia.

METHODS

The study protocol adhered to the tenets of the Declaration of Helsinki and informed consent was obtained from the parents of children enrolled in the study and an ethics committee approval was sought. Children with a documented progression of myopia of ≥0.5 diopters, with a minimum follow-up of 3 months, aged between 2 and 15 years were recruited consecutively for 2 years from June 2018. Children with congenital high myopia, pathological myopia, who had undergone ocular surgery, who were using other drugs or contact lenses, and whose parents did not provide informed consent for participation were excluded from the study. Each child underwent a detailed ophthalmic examination that included assessment of the best-corrected visual acuity, anterior segment assessment using slit-lamp biomicroscopy, and posterior segment assessments after pupillary dilatation. Every child underwent cycloplegic refraction before starting the drops and the change in refraction was confirmed. Parents of eligible children were counseled in the native language regarding the use of atropine 0.01% eye drops to retard the progression of myopia. They were briefed about the current available studies and the benefits and an informed decision involving the parents were made before starting the medication. Parents were advised to administer one drop of the drug once daily in both eyes at bedtime. The method of administration (child in supine position with the creation of a lower lid pouch) was also explained and anticipated common side effects like photophobia, blurring, flu-like symptoms, or rashes, etc.,). Parents and children were asked to self-report at any stage if they perceived any side effects. It was planned to use the drops for a minimum of 2 years before stopping the drug.

Enrolled children were followed up at 1 month after the start of the drug and thereafter at 4-month intervals for 2 years till August 2020. Each child was assessed for the best corrected distant and near vision at each visit and parents were enquired regarding adverse effects and difficulty in near work on using the drug.

Statistical analysis

Data were entered into a Micro Soft Excel Spreadsheet and then exported to the STATA statistical software version 14.0 (College station , Texas , USA) for further analysis. Continuous variables were expressed as mean (standard deviation) and categorical variables as proportions. The change in mean spherical equivalent was assessed using a paired *t*-test and a pairwise correlation test. A $P < 0.05$ was considered significant.

RESULTS

Parental counseling was provided to 57 children that were considered eligible for enrolment in the study. Ten parents opted out of the study and the remaining 47 (82.46%) children were enrolled in the study. Twenty (42.55%) children were lost to follow-up after the initial dose and were excluded from further study. Of the patients who were lost to follow-up, 7 were male (35%) and 13 were female (65%) and the mean age was 11.7 years ± 2.5 years (range 5–15 years). Three participants were lost to follow-up after the initial 2 months of usage and the rest of them did not follow-up after prescribing the drops. The mean age of the remaining 27 children was 9.04 ± 3.05 years (range 2–14 years) and most ($n = 13$, 48.1%) were aged 5–10 years and were female ($n = 17$, 62.96%). The mean age of dropouts was significantly higher than the children who continued in the study ($P = 0.003$). The mean duration of follow-up of the study participants was 10.8 ± 5.1 months with a minimum follow-up of 3 months and maximum of 23 months.

The mean change spherical equivalent at the last follow-up of 54 eyes of 27 children is shown in Table 1. The overall

Table 1: Change in spherical equivalent from baseline to last follow-up in the study population

Mean spherical equivalent		Paired samples statistics			Paired differences			
		n	SD	Correlation	*P*	Mean±SD	*t*	Significance (two-tailed)
Mean spherical equivalent right eye								
At start of atropine 0.01%	−5.3500	27	3.32644	0.991	<0.001	0.344±0.464	3.852	0.001
At the end of last follow-up	−5.6944	27	3.38573					
Mean spherical equivalent left eye								
At start of atropine 0.01%	−5.2315	27	3.057	0.985	<0.001	0.314±0.539	3.031	0.005
At the end of last follow-up	−5.55	27	3.124					

SD - Standard deviation

change in the mean spherical equivalent from baseline to last follow-up was 0.329 by the paired sample *t*-test ($P < 0.001$). Twenty-two of the children had more than 6 months of follow-up and 15 eyes (34.09%) showed an increase of spherical equivalent change of ≥0.5 diopters and 4 zeyes (9.09%) showed an increase of ≥1 dioptre. Overall, twelve (44.44%) of the 27 children progression of myopia despite atropine 0.01% use.

None of the patients including those who stopped the drug after 2 months reported any of the above-mentioned adverse effects. A treatment-related event was reported in one patient who procured atropine 1% drops instead of 0.01%, despite having a correct prescription which resulted in difficulty in reading for 2 weeks.

DISCUSSION

Antimuscarinic topical medications have been shown to be effective in slowing myopia progression in children and multifocal lenses may confer a minimal benefit. Orthokeratology contact lenses do not modify refractive error but may be effective in slowing axial elongation. The review found very low certainty evidence regarding rigid gas permeable contact lenses and spherical aberration contact lenses to slow the progression of myopia.[10]

Donders introduced the concept of atropine in the treatment of myopia as he hypothesized that spasms of accommodation in myopic patients are the reason for progression.[17] Pollock was the first to use atropine in the treatment of myopia.[18] The exact mechanism of action of atropine in retarding myopia progression is not clear though several postulates have been put forward. One theory is that atropine acts on the retina or sclera regulating the growth by preventing the thinning or stretching.[19-21] Several studies have attributed myopia to reading and doing near work uninterruptedly.[22-27] The Singapore Cohort Study of the Risk Factors for Myopia and the Orinda Longitudinal Study of Myopia reported that reading, playing video games, and watching television was not a significant risk factor for myopia and showed that parental history was an important association and increased outdoor activity had a beneficial effect on myopia.[22,28] Two additional factors that have incidentally happened for our study are an increased time of online teaching and increased use of gadgets (>2 h in most children) due to the pandemic during the latter half of follow-up that has also reduced outdoor activity. These factors were not included as a parameter as they occurred midway through the follow-up period.

Efficacy of the drug

The use of low concentration atropine (0.01%) has become widely accepted[14] after the ATOM 2 study showed a progression rate of −0.49 ± 0.63 D in 2 years. A case-control study among Caucasians in the United States found a rate of myopic progression of −0.1 ± 0.6 D/year in the atropine 0.01% group. Several studies currently provide evidence on the efficacy of low-dose atropine.[11,29,30] Our study also shows a mean change in the spherical equivalent of 0.329 ± 0.49 D between the last and the first follow-up which is comparable to previous studies. Previous studies have recommended that retreatment with atropine 0.01% can be equally effective as the primary treatment and clinicians must titrate treatment by stopping and restarting treatment according to individual progression rates.[14]

A study by Sacchi, *et al*.,[31] reported that 21% of patients progressed despite the usage of the drug while 24% of participants in the ATOM 2 study[32] showed progression of myopia. The rate of progression in our series (44%) is significantly higher than in those studies. There are reports that some children are nonresponders to lower doses of atropine suggesting higher doses to be considered after weighing dosage-related adverse effects.[9,32]

Limitations of the study

The increased progression rates in our study may be due to small sample size, varied periods of follow-up or because of an ethnic difference and needs more detailed evaluation. It is also possible that the increased use of digital devices for longer times and restricted outdoor activity during

the pandemic have influenced the rates and degree of progression. However, we are not able to comment on that as part of this study.

Adherence to treatment, safety, and follow-up

In our study, the children were included in accordance with the ATOM 2 study[32] criteria and we have included the spherical equivalent at the start and end of the follow-up period with a minimum of 3 months follow-up. In the study conducted by Diaz-Llopis *et al*. in 2018, the dropout rate from the treatment group was 53.5%.[33] In our study, 42.55% of children dropped out of the study, and part of the follow-up period coincided with the COVID 19 pandemic. Even though the dropout rates are comparable, the fact that the rest of the patients have continued the treatment despite the pandemic and with good adherence (not more than 2 missed doses/month) is a welcome sign.

None of the patients in our study who were followed up had any adverse effects, except for one patient who used 1%. Atropine drops instead of the prescribed 0.01%. Sacchi *et al*. reported side effects like photophobia, in 9.2% of the patients who were followed up.[31] Two patients reported nonavailability of the drug during the pandemic, but they were able to procure it and did not affect the adherence.

Patient acceptance of a new treatment

Ten (17.5%) of the 57 children who were advised to start atropine treatment did not start the treatment. The reasons included practical difficulty and apprehension of using the drug for a long time, personal views on various treatment methods, and the availability of various nonevidence-based alternative treatments prevalent in the community. Many parents and children were more concerned about the cosmetic aspect of wearing glasses than the progression of myopia. These are cultural differences which have to be included in charting treatment plans. For a treatment option to be acceptable, it has to be consistent with lifestyle, appropriate for managing the problem, easy to apply, and effective.[34] Hence to make a treatment preference and acceptance valid, the caretakers have to be presented with information on each treatment enhancing their understanding, assessing their perceptions, and discussing their treatment choices.[35] The hurdles faced in our study during parental counseling were the ambiguous areas regarding treatment like the optimal time to start and stop and duration of any retreatment if needed.

CONCLUSION

The studies till date on the efficacy of atropine have shown consistent and comparable results on retardation of progression of myopia and that low-dose atropine is as effective as the higher concentration,[29,30] but there are many facets untouched which remain to be clarified like optimal age, duration of treatment, management of nonresponders including criteria to define nonresponders, whether 0.01% is suitable for all ages or higher concentrations are needed and whether there is a racial or ethnic difference in the response.

Recommendations

Patient treatment preference must be modified by parental education and assessing parental preference before starting treatment which will help in further evaluating this promising treatment and provide further clarity to the protocols. Future studies that bring out the role of environmental factors which modify the effect of low-dose atropine may also be worthwhile.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Diabetic nephropathy may predict the retinal changes of patients with diabetes: An Indian population-based study

ABSTRACT

Purpose: This study aimed to study and correlate fundus changes in patients with Type 2 diabetes mellitus with different stages of nephropathy. **Materials and Methods:** It is a prospective, observational study involving 100 patients at a tertiary health-care institute. Type 2 diabetic patients with diabetic nephropathy (DN) were enrolled. Those with uncontrolled hypertension, history of other ocular diseases, or surgeries were excluded. DN was defined as – microalbuminuria, macroproteinuria, and massive proteinuria based on 24-h urine protein analyser values. Participants underwent complete ophthalmic examination with fundus examination, fundus fluorescein angiography, and optical coherence tomography and were graded into various stages of diabetic retinopathy. The influence of nephropathy on retinal changes was assessed using Pearson's correlation analysis. **Results:** The study population included those with a median age of 56 years (range 38–79 years). In the group with microalbuminuria, 10 (62%) eyes did not have any retinopathy changes. In the macroproteinuria group, 61 (53%) showed mild-to-moderate nonproliferative diabetic retinopathy (PDR). In addition, 30 eyes of patients (48%) with massive proteinuria had PDR which were all statistically significant. Also in 32 eyes (16%) of DN patients, clinically significant macular edema was present, most of which, i.e., 24 (75%), were in the macroproteinuria group. **Conclusions:** These findings indicated that the severity of proteinuria was significantly associated with fundus changes in Type 2 diabetic patients. Thus, we conclude that DN is a marker of retinopathy and timely ophthalmic evaluation of patients should be done.

Keywords: Diabetes, diabetic nephropathy, diabetic retinopathy, fundus, glycated hemoglobin

INTRODUCTION

Diabetes Mellitus (DM) is one of the leading causes of blindness worldwide. At present, India has about a million diabetics.[1] Rising prevalence requires proper study to assess diabetics and its related complications. There has been a multifold rise in cases of DM in the COVID-19 pandemic, especially with restriction of movement due to lockdowns, work from homes and decreased exercise including running, gym and use of steroids.[2,3] Lack of exercise and improper diet caused by poor availability of healthy food along with psychological stress may lead to significant weight gain and thereby DM.[4]

Diabetes is a systemic disease and may lead to various micro and macrovascular complications such as diabetic retinopathy (DR), diabetic nephropathy (DN), and peripheral neuropathy. It is estimated that within 15–20 years of diagnosis, more than 75% of diabetic patients develop DR.[5] Approximately 40% of people with diabetes develop DN which has become the leading cause of end-stage renal disease in many countries.[6-8] Globally, the number of people with DR will grow from 126.6 million in 2010 to 191.0 million by 2030, and the number with vision-threatening diabetic retinopathy will increase from 37.3 to 56.3 million if prompt action is not taken.[9]

Although prevalence and risk factor for DR in Type 2 diabetes is extensively studied,[10-12] there are fewer data

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correlating DR and DN; with no major studies in the Indian population. Therefore, the current study strived to investigate relationship between changes of DR and its severity in patients with different stages of DN.

MATERIALS AND METHODS

It was a prospective observational study done at the department of ophthalmology of a tertiary health-care institute. The study protocol was reviewed and approved by the institute ethics committee. Written informed consent was obtained from all individual participants before the start of the study.

The study was conducted on a total of 100 patients (195 eyes). Patients with DN due to Type 2 diabetes were included in the study. Patients with cardiovascular disease, malignancy, pregnancy, and acute intercurrent illness who could otherwise have non-DN were excluded. In addition, patients with a previous history of laser photocoagulation, glaucomatous and myopic patients, and other retinal vascular and proliferative diseases were excluded.

Patients underwent blood profile tests including serum creatinine, urine albumin excretion, blood pressure, fasting blood glucose, glycated hemoglobin (HbA1C), and detailed ophthalmic examination. They were divided into three groups – microalbuminuria (urinary albumin excretion of 30–300 mg/day), macroproteinuria (urinary albumin excretion of ≥300 mg/day), and massive proteinuria (urinary albumin excretion of ≥3000 mg/day) based on 24-h urine protein values using urine protein analyzer. At the time of enrolment in the study, a complete medical and ocular history was taken along with a comprehensive ophthalmic examination. Their fundus examination was done using fundus photography, fundus fluorescein angiography, and optical coherence tomography. It was then graded into no DR, mild, moderate-to-severe non-PDR (NPDR) and PDR. Diabetic macular edema was categorized into clinically significant macular edema (CSME) and non-CSME.

Statistical analysis was performed on SPSS version 24 and STATA 12.1 (StataCorp, College Station, TX). Median values were used to present continuous variables, while categorical variables were expressed as numbers or percentage values. Comparisons between continuous data were performed using the Mann–Whitney *U*-test. A Chi-square (χ^2) test was used to analyze the differences between categorical data. Statistical significance was established for results with a $P < 0.05$.

RESULTS

The study was done in 100 patients (195 eyes) with a median age of 56 years (range 38–79 years). Out of 100 patients, 63 were male and 37 were female. The duration of diabetes ranged from 1 to 35 years. Forty-seven patients had diabetes for more than 10 years. About 77% of patients had associated hypertension (HTN). In five of the total eyes, fundus could not be visualized due to the presence of advanced cataracts in 4 of them and total corneal opacity in one. Seventy-one patients were on insulin, and the rest 29 were on oral hypoglycemic drugs.

In our study, of the 195 eyes screened, 51 (26%) showed no signs of DR, 50 (25%) showed mild NPDR, 41 (21%) had moderate NPDR, 14 (7%) had severe NPDR, and 39 (20%) had PDR. Furthermore, based on 24-h urine protein analysis, the majority, i.e., 60% of patients, had proteinuria between 300 and 3000 mg/24 h and a significant proportion, i.e., 32%, had massive proteinuria. Only 8% of patients had microalbuminuria.

The majority, i.e., 10 (62.5%), eyes of patients with microalbuminuria had no changes of DR, four (24%) had mild-to-moderate NPDR, while the remaining two (12.5%) had PDR. Amongst those who had macroproteinuria, of them 41 eyes (35.3%) had no DR changes, 33 (28.4%) had mild NPDR, 28 (24.1%) had moderate NPDR, seven (6%) had severe NPDR, and the remaining seven (6%) had PDR changes. All patients with massive proteinuria had some form of DR, i.e., 15 (23.8%) had mild NPDR, 11 (17.4%) had moderate NPDR, seven (11.1%) had severe NPDR, while almost half of them, i.e., 47.6%, had PDR. The relationship between proteinuria and retinopathy was found to be statistically significant ($P < 0.001$) [Figure 1].

In addition, out of sixteen patients with microalbuminuria, only 3 had maculopathy. Among patients with macroproteinuria, 24 had CSME, and four had non-CSME maculopathy. In massive proteinuria group, eight patients had maculopathy [Figure 2].

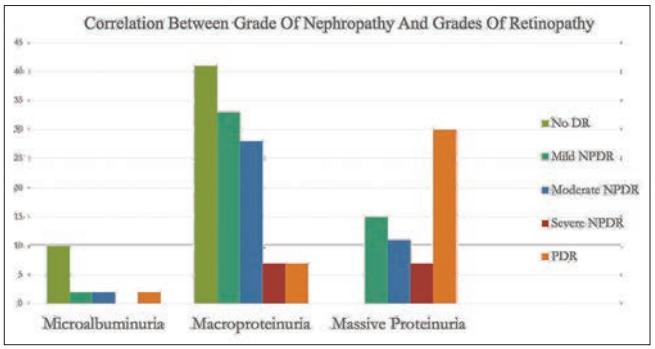


Figure 1: Graphical correlation between grades of nephropathy and grades of retinopathy

In our study, 48% of patients had DR of >10 years duration and 36% of 5–10 years duration. Furthermore, 87% of patients had uncontrolled diabetes (HbA1C >7). We also found a positive relationship between severity of diabetes (HbA1C) and duration of DM with the stage of DR [Figure 3].

DISCUSSION

DR and DN are microvascular complications in which retina and glomerulus are affected respectively by similar pathophysiologic features in diabetes. Chronic hyperglycemia is the inciting factor.[13,14] It causes progressive narrowing and eventual occlusion of vascular lumina, subsequently leading to inadequate perfusion of the affected tissue. In the retina, diabetes induces programmed cell death of Muller, ganglion cells, pericytes, and endothelial cells.[15] In the glomerulus, urinary protein loss and renal function decline are associated with widespread capillary occlusion and podocyte loss.

Several risk factors appear to influence susceptibility to the microvascular complications of DM, but the roles of genetic and environmental factors are not yet completely understood. In most of the previous studies, the prevalence of microvascular complications in patients with DM was evaluated along with their association with both univariate and multivariate regression analyses.[16] However, the relationship of one diabetic microvascular complication with another, to date, has not been clearly described in the Indian population. Although there has been consistent correlation showing association of risk factors like DM duration, poor glycemic control, arterial HTN, and poor lipid control with DR and DN,[17,18] especially in Type 1 diabetics; however, the correlation is less evident in Type 2 diabetics with different prevalence rates.[19]

Pedro *et al*. showed that for DR, microalbuminuria is a good predictor for Type 1 DM but not for Type 2. However, their study showed a significant relationship of overt nephropathy with DR and macular edema in both types of diabetes.[20]

In the current study, 10 (62%) eyes in the group with microalbuminuria did not have any retinopathy changes. In the macroproteinuria group, a significant portion of patients' eyes, i.e., 61 (53%), showed mild-to-moderate NPDR. In massive proteinuria, 30 eyes of patients (48%) had PDR, which is again a significant number. Thus, there was a positive relationship found between proteinuria and retinopathy which was statistically significant. El-Asrar *et al*.[21] indicated that the prevalence of DN was found to rise with increasing severity of DR. Schmechel and Heinrich also indicated that the prevalence of proteinuria increased relative to the severity of DR in Type 1 and Type 2 DM.[22]

Also out of the total, CSME was present in 32 eyes (16%), most of which, i.e., 24 (75%), were in the macroproteinuria group. This is consistent with previous studies where the prevalence rates of DN was significantly higher among patients with DME when compared with those without DR.[21] However in a study by Lee *et al*., there was no significant association between CSME and DN, though they limited this finding by their smaller sample size, especially in patients with CSME.[23]

In addition, we found a significant relationship between HbA1C and both retinopathy and nephropathy as HbA1C assesses the glycemic control in diabetic, both in univariate and bivariate regression analyses. This result is consistent with previous studies where HbA1c, DM duration, and blood pressure were the most important risk factors.[24]

Similar previous studies showed diverse conclusions, and thus, they all were not consistent with the results of the current study. It may be due to differences in the study design, smaller sample size, or ethnic differences between east and western populations compared with the previous studies.

Our study concluded that the prevalence of diabetic retinopathy and maculopathy was more in patients with macroproteinuria and massive proteinuria than with microalbuminuria. Furthermore, a high prevalence of PDR

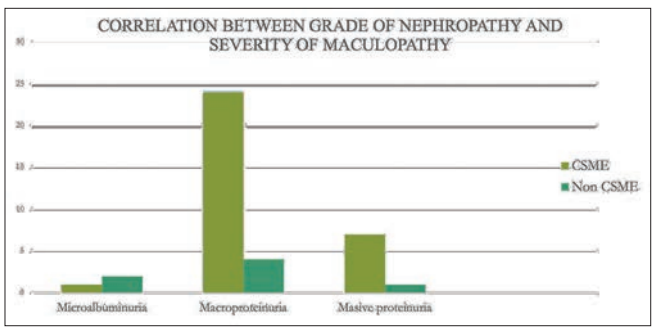


Figure 2: Graphical correlation between grades of nephropathy and grades of maculopathy

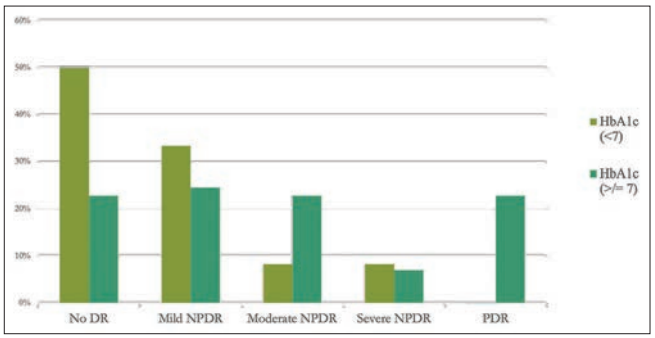


Figure 3: Correlation between severity of diabetic retinopathy and control diabetes

was seen in patients with massive proteinuria. Thus, there was a positive correlation between diabetic retinopathy and nephropathy in Type 2 diabetics.

There also have been some previous studies that have reported the occurrence of DN and DR in isolation with no association between them.[25] This may be explained by fundamental differences in some patients and in pathogenesis. Further experimental studies would be required to investigate the exact differences in the pathophysiology of these diabetic microvascular complications.[26]

CONCLUSIONS

A number of studies conducted on the western population provide evidence that DR is a powerful predictor for the progression of renal damage in DM patients, as it may be independently associated with the development of microalbuminuria.[21,27-29] To the best of our knowledge, this is the first study evaluating the relationship between DR and DN in a Indian population and predicting the presence and severity of DR according to the severity of DN. The study suggests that patients with diabetic proteinuria must be carefully monitored for progressive eye disease, and timely evaluation should be done for a better prognosis. Thus, this study will help us to better understand the microvascular damage in diabetes and improve ways to screen, treat and control the disease.

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Conflicts of interest
There are no conflicts of interest.

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Original Article

A comparative study on ocular manifestations in patients with polycystic ovary syndrome and healthy volunteers

ABSTRACT

Background: Polycystic ovary syndrome is a common endocrinological disorder of females in the reproductive age group.It can produce changes in the ocular tissues and thereby affect vision.In this study,we aim to compare intraocular pressure, central corneal thickness, central macular thickness, retinal nerve fiber layer thickness, Schirmers test and tear break up time between the eyes of women with and without PCOS. **Methods and Material:** This study included 60 eye of 30 women with PCOS(Group 1) and 60 eyes of 30 healthy women (Group 2). Intraocular pressures (IOP) were assessed using Goldman applanation tonometry, central corneal thickness (CCT) using pachymeter, retinal nerve fiber layer (RNFL) and central macular thickness (CMT) using optical coherence tomography (OCT), Schirmers test using standardized strips and tear break up time (TBUT) were assessed for all women. **Results:** The Mean Central Corneal Thickness, average RNFL, superior average RNFL and nasal average RNFL thicknesses were higher in patients with PCOS than in healthy women (all $p<0.01$) respectively. Schirmers test results and Tear Break Up Time values were significantly lower in the PCOS group (both $p<0.01$). The mean IOP and CMT were similar between the 2 groups. Duration of the disease was weakly positively correlated with CCT and superior RNFL and moderately positively correlated with average RNFL. **Conclusions:** Women with PCOS had significant increase in central corneal and retinal nerve fiber layer (average, superior, nasal quadrant) thickness and a significant decrease in Schirmer test and TBUT values. It is advisable that all women with PCOS undergo an eye examination for dry eye. Hormonal regulations prior to corneal and refractive surgeries may help improve outcomes.

Keywords: Central corneal thickness, polycystic ovarian syndrome, retinal nerve fiber layer thickness, Schirmer's test, tear breakup time

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a common endocrinological disorder that affects an estimated 4%–10% women of reproductive age.[1] PCOS is associated with menstrual irregularities, ovulatory dysfunction, and symptoms associated with hyperandrogenism.[2,3]

In recent years, various studies have reported the presence of sex hormone receptors in various ocular tissues.[4] PCOS can lead to changes in the ocular tissue and thereby affect the visual functions of these patients.[4] We designed a cross-sectional study to determine the magnitude of retinal and other ocular

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changes in women with PCOS presenting to the ophthalmology department of a tertiary care teaching hospital in central Kerala.

SUBJECTS AND METHODS

The study protocol was approved by the institutional ethics and research committee, and written informed consent was obtained from all participants before the enrolment in the study. Sixty women were enrolled in the study over a period of 18 months between January 2020 and June 2021. This included thirty patients with PCOS who were recruited from the Department of Obstetrics and Gynaecology at the study institute after confirming the diagnosis of PCOS.

PCOS was defined based on the 2003 Rotterdam criteria[5] that included the following:

a. Oligomenorrhea/amenorrhea
b. Clinical and/or biochemical findings of hyperandrogenism
c. Polycystic ovaries assessed on ultrasonography (existence of 12 or more follicles 2–9 mm in diameter in ovaries).

At least two out of the three criteria must be fulfilled for the diagnosis of PCOS. Thirty age-matched healthy females who presented to the ophthalmology department without any gynecological symptomatology, without PCOS, and with normal menstrual cycles were recruited as the comparator group.

This study excluded females with other endocrine disorders, impairment of hepatic and/or renal function, chronic use of drugs that can interfere with the metabolism of carbohydrates, lipids and with renal function (diuretics, antihypertensives, antilipidemics, and corticosteroids), use of Oral contraceptive pills (OCPs), smoking, alcohol, illicit drug use, any eye disorders including high myopes, history of intraocular surgeries.

A detailed medical history that included their age, personal, and family history was collected from each participant. The best-corrected visual acuity was estimated using Snellen chart. A detailed slit-lamp assessment of the anterior segment was done, and intraocular pressures (IOPs) were measured using a Goldmann applanation tonometer. Posterior segment assessments were done using indirect ophthalmoscopy with a 20D lens. The central corneal thickness (CCT) was measured using a pachymeter (full auto tonometer TX-20P Canon). The central macular thickness (CMT) and retinal nerve fiber layer (RNFL) assessments (all sectors) were done using optical coherence tomography (OCT) Cirrhus high definition OCT (Cirrhus HD OCT).

All patients underwent Schirmer's and tear breakup time (TBUT) test. An abnormal Schirmer's test was defined as soaking of Schirmer's strip <6 mm in 5 min. The tear film was examined at the slit lamp under cobalt blue filter in the TBUT test. An abnormal TBUT test was defined as an interval of <10 s between an eye blink and first appearance of a dry spot on the ocular surface.

The mean of continuous variables was compared using an independent sample *t*-test, and categorical variables were compared using a Chi-square test. A $P < 0.05$ was considered as statistical significance.

RESULTS

The study included a total of 120 eyes from 30 patients in the PCOS group and 30 individuals in the control group. The mean age ± standard deviation of women with PCOS (25.73 ± 3.27 years) did not differ significantly ($P = 0.582$) from women without PCOS (26.20 ± 3.27 years) in the study population.

The mean IOP values in the PCOS group and control group were 15.51 ± 2.04 mmHg and 15.57 ± 2.89 mmHg, respectively ($P = 0.896$). The average CCT in PCOS group (555.13 ± 13.16 ∝m) was significantly higher ($P < 0.01$) than the control group (523.05 ± 13.93 ∝m). The mean value

Table 1: Comparison of study parameters between PCOS and control group

Parameters	Group	*n*	Mean±SD	*t*	*P*
Age	1	30	25.73±3.27	0.553	0.582
	2	30	26.20±3.27	0.553	0.582
IOP	1	60	15.52±2.04	0.131	0.896
	2	60	15.58±2.89	0.131	0.896
CCT	1	60	555.13±13.16	12.971	<0.01
	2	60	523.05±13.93	12.971	<0.01
SRNFL	1	60	124.85±5.39	9.055	<0.01
	2	60	116.65±4.49	9.055	<0.01
IRNFL	1	60	126.27±11.30	0.008	0.993
	2	60	126.28±10.44	0.008	0.993
NRNFL	1	60	77.52±11.23	4.213	<0.01
	2	60	69.73±8.87	4.213	<0.01
TRNFL	1	60	61.33±6.33	1.463	0.146
	2	60	59.75±5.50	1.463	0.146
Average RNFL	1	60	97.53±4.93	5.316	<0.01
	2	60	93.18±3.99	5.316	<0.01
CMT	1	60	234.42±16.51	0.235	0.815
	2	60	235.08±14.53	0.235	0.815
Schirmer	1	60	10.77±1.77	17.604	<0.01
	2	60	16.53±1.81	17.604	<0.01
TBUT	1	60	10.24±2.30	14.083	<0.01
	2	60	16.27±2.40	14.083	<0.01

S: Superior, I: Inferior, N: Nasal, T: Temporal, RNFL: Retinal nerve fiber layer, SRNFL: Superior RNFL, IRNFL: Inferior RNFL, NRNFL: Nasal RNFL, TRNFL: Temporal RNFL, CMT: Central macular thickness, IOP: Intraocular pressure, CCT: Central corneal thickness, TBUT: Tear breakup time, SD: Standard deviation

Table 2: Comparison of retinal nerve fiber layer thickness with other studies

Groups compared/study Group 1 versus group 2	Average thickness		Superior quadrant		Inferior quadrant		Nasal quadrant		Temporal quadrant	
	1	2	1	2	1	2	1	2	1	2
Our study	97.53	93.18	124.85	116.65	126.27	126.28	77.52	69.73	61.33	59.75
Teberik K *et al*.	-	-	114	133.9	119.8	117.5	79.4	73.8	68.2	69
Mehemet Demir *et al*.	109.8	103.96	111.55	105.39	108.32	102.64	-	-	-	-
Jose Edvan D Souza *et al*.	101.2	98	128	120	135	130.6	75.8	77.6	66.3	65.4

Table 3: Comparison of central corneal thickness, Schirmer's test, tear breakup time values with other studies

Groups compared/study Group 1 versus group 2	CCT		Schirmer's test		TBUT	
	1	2	1	2	1	2
Our study	555.13	523.05	10.77	16.53	10.24	16.27
Hakan Coksuer *et al*.	-	-	19.9	18.8	8.6	11.3
Karaca Adiyeke *et al*.	550.60	518.40	10.80	16.74	11.10	14.64
M. Demir *et al*.	556.75	551.88	-	-	-	-

CCT: Central corneal thickness, TBUT: Tear breakup time

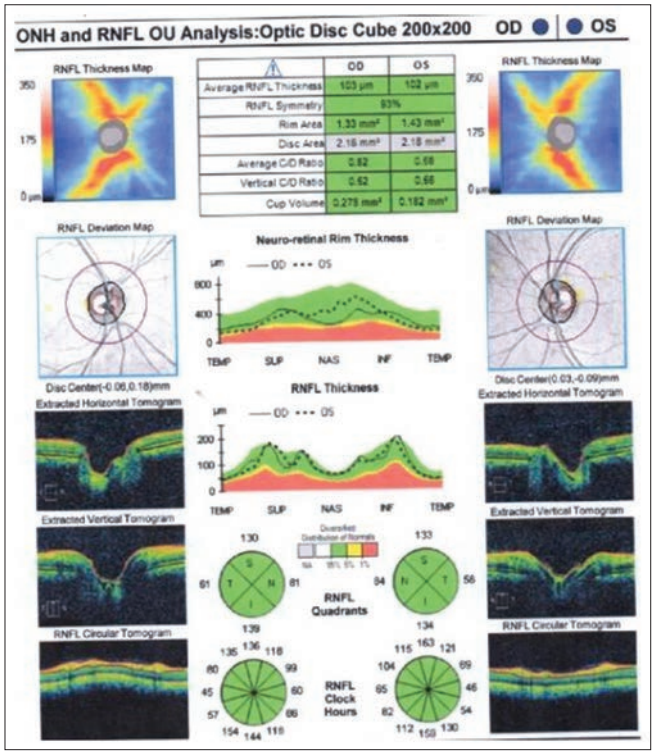


Figure 1: Optical coherence tomography optic disc showing normal retinal nerve fiber layer thickness

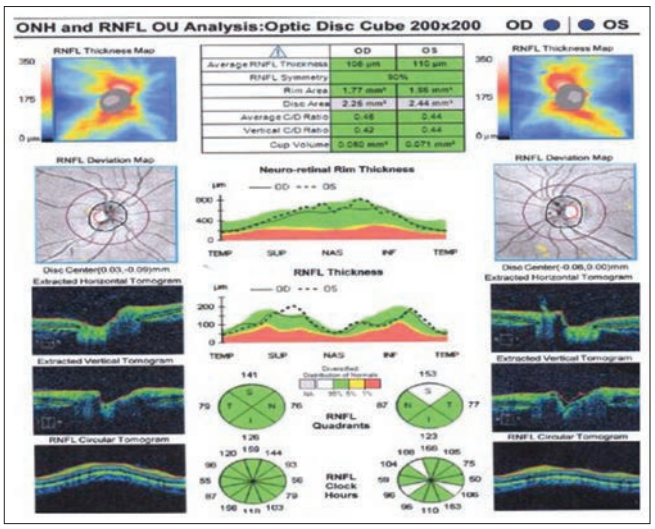


Figure 2: Optical coherence tomography optic disc showing increased superior retinal nerve fiber layer thickness in polycystic ovarian syndrome patients

of the superior, nasal, and average RNFL thickness was significantly higher in the women with PCOS [Table 1]. No statistically significant difference ($P = 0.815$) was found between both the groups in terms of CMT.

The PCOS group had significantly lower mean Schirmer's test value and shorter TBUT compared to the control group [Table 1].

Duration of the disease showed a statistically significant weak positive correlation with CCT ($r = 0.289$) and superior RNFL ($r = 0.319$) and a moderate positive correlation with average RNFL ($r = 0.379$) [Figures 4-6].

DISCUSSION

PCOS is a common endocrinological disorder among women of reproductive age group. It is also known as hyperandrogenic ovulation or Stein-Leventhal syndrome. Several studies have shown the presence of Sex steroid hormones (SSH) (estrogen, progesterone, and androgen) receptors in various ocular tissues such as retina, lens, ciliary body, iris stroma, choroid, lacrimal gland, meibomian gland, palpebral, and bulbar conjunctiva.[6] The elevated sex steroid levels in PCOS can affect the physiopathogenesis of the ocular tissue similar to the cardiovascular system and the endometrium.[7]

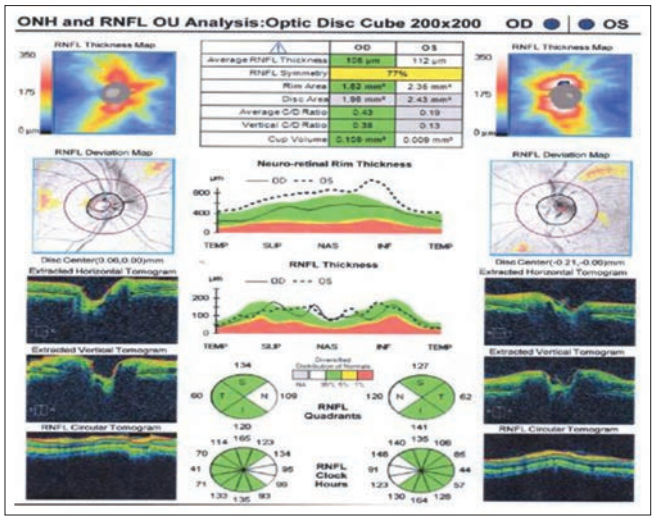


Figure 3: Optical coherence tomography optic disc showing increased nasal retinal nerve fiber layer thickness in polycystic ovarian syndrome patients

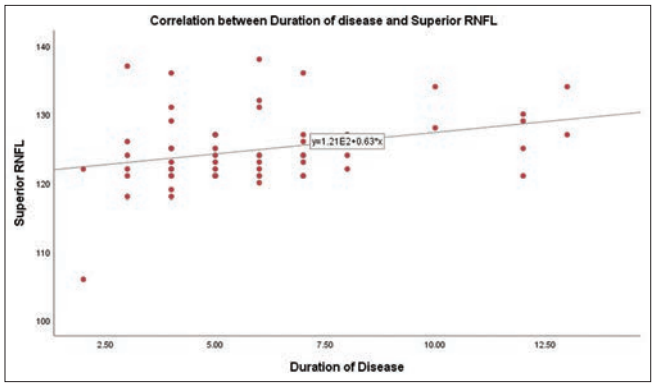


Figure 5: Correlation between duration of disease and superior retinal nerve fiber layer

We found that the CCT was significantly higher in the PCOS group than the control group. No significant difference was found between both the groups in terms of mean values of IOP and CMT. Furthermore, the average RNFL, average superior, and nasal RNFL thickness were significantly higher in women with PCOS than in healthy women. Figure 1 shows optical coherence tomography of optic nerve head with normal retinal nerve fibre layer thickness in all quadrants. Figure 2 and 3 shows increased retinal nerve fibre layer thickness in the superior and nasal quadrants in PCOS patients. The PCOS group also had a significantly lower mean Schirmer's test value and shorter TBUT than the control group.

Gonadal hormones play a major role in the homeostasis of the cornea through effects that are mediated by alpha and beta estrogen, progesterone, and androgen receptors in the nuclei of human corneal epithelial, stromal, and endothelial cells.[8-10] Corneal thickness fluctuates with variations in the sex hormone levels, especially during ovulation and luteal

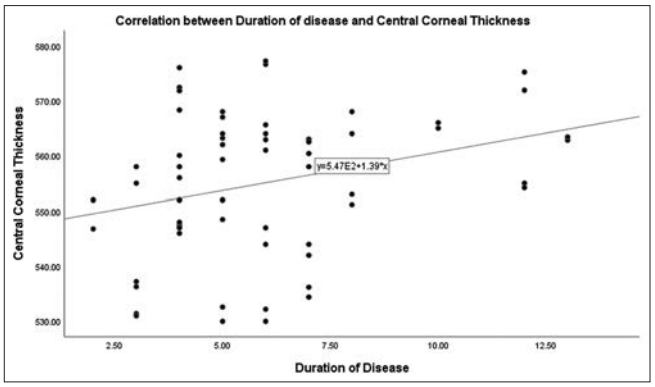


Figure 4: Correlation between duration of disease and central corneal thickness

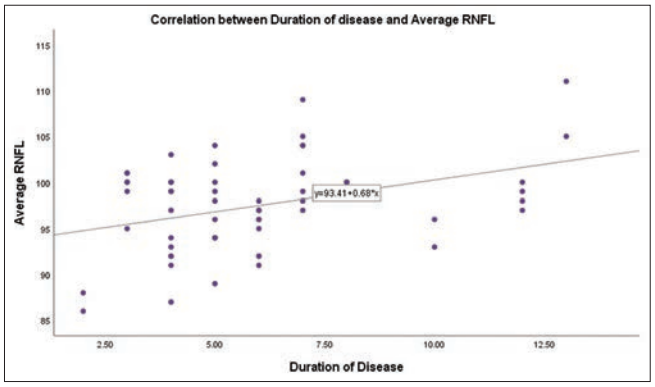


Figure 6: Correlation between duration of disease and average retinal nerve fiber layer

phase of menstrual cycle where there is a significant increase in the estrogen levels.[11,12] A study by Kiely *et al*.[13] reported that a rise in the estrogen levels during the menstrual cycle was associated with an increase in the corneal thickness. Similar to our study, a significant increase in the CCT in PCOS patients was reported by Kebapcilar *et al*.[14] The main reasons for these changes include: (1) insulin-like growth factor 1 induced inhibition of the corneal endothelial pump and increased endothelial permeability[14] and (2) enhanced sodium reabsorption into the corneal tissues due to elevated androgen levels leading to water retention and corneal edema.[15] However, a study by Demir *et al*.[16] showed no significant difference in CCT between PCOS patients and normal women.

Different parts of the retina respond differently to the effects of androgenic hormones. Table 2 shows the comparison of RNFL thickness with other studies. In the current study, the RNFL thickness was found to be significantly higher in the superior and nasal quadrants in the PCOS patients when compared to normal healthy women. In a similar study conducted by Demir *et al*.,[16] the RNFL thickness in the nasal and superotemporal quadrants of PCOS patients was found to be significantly higher in PCOS patients than the control

group. A study performed by Açmaz *et al*.[17] also showed similar results with a significantly higher nasal RNFL thickness in PCOS patients when compared to control group. This can be explained by the neurotrophic action of androgens, which are increased in the PCOS patients.[18] Furthermore, hyperandrogenism in PCOS patients leads to elevated levels of nerve growth factor which is needed for ovarian follicular growth.[19]

Sex hormonal variations can influence the tear function since these hormonal receptors are found in many components of the tear film: lacrimal gland, conjunctiva, goblet cells and their mucin products, the meibomian glands, and the cornea. Estrogen is an antagonist of meibomian gland function, and increased levels of estrogen in PCOS patients can lead to meibomian gland dysfunction and evaporative dry eye and visual impairment.[20] Previous studies have reported lower Schirmer's test values, shorter TBUT, and increased incidence of dry eye in PCOS patients.[20,21] Consistent with the previous studies, the current study also demonstrated a statistically significant lower Schirmer's test value and shorter TBUT in PCOS patients when compared to healthy women. Table 3 shows the comparison of central corneal thickness, Schirmers test and Tear Break Up Time test values with other studies.

The lack of pathological examinations is a limitation of the study. The study was done at a single center and may limit generalizability of these results. Further studies on population of women with PCOS from diverse settings can help to further validate these associations.

CONCLUSION

Women with PCOS had significant increase in central corneal and RNFL (average, superior, and nasal quadrant) thickness and a significant decrease in Schirmer's test and TBUT values. Our findings suggest that patients diagnosed with PCOS should undergo ophthalmic examination for the diagnosis and treatment of dry eye. Ophthalmologists must consider adequate precautionary measures, including hormonal regulations before corneal surgeries (LASIK, penetrating keratoplasty) in women with PCOS. More extensive research is recommended to obtain further details regarding the ocular manifestations of PCOS.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Fish hook injury to the eye: A unique presentation

ABSTRACT

Fish-hook injuries are relatively uncommon and frequently involve upper extremities. A wide spectrum of ocular and adnexal trauma can occur following fish hook injury. We report an unusual presentation of ocular adnexal injury in a 34-year-old male who presented with a fish hook embedded in the lower eyelid margin with an intact anterior and posterior lamella. The fish hook was retrieved successfully without traumatizing both the lamellae by adopting a "sutureless, gray line split technique." This case is being reported for its distinctive presentation and to emphasize the need to respect tissue anatomy and minimize surgical trauma while attempting removal of such sharp objects in order to achieve optimal functional and aesthetic outcomes.

Keywords: Eyelid injury, fish hook, gray line split technique, sutureless

INTRODUCTION

Fishing is considered a common leisure activity across the world, andit is a major source of income and livelihood, especially in the coastal regions of India. Ocular and adnexal trauma with fish hooks, though rare, can be sight threatening as in penetrating globe injury or nonsight threatening as in adnexal injury. We discuss an unusual case of fish hook injury ofthe eyelid margin with intact anterior and posterior lamella. This is the first case of fish hook injury repair using the "gray line split-cut it out" technique being reported.

CASE HISTORY

A 34 years old male presented with history of left lower eyelid pain and foreign body sensation following injury with a barbed fish hook 4h ago while watching his friend fishing. Ocular examination revealed best corrected visual acuity (BCVA) of LogMAR 0.00 in both the eyes. A fish hook foreign body was found to be trapped at the junction of medial two-thirds and lateral one-third of the left lower eyelid margin through a point entry posterior to the gray line [Figure 1a]. The overlying anterior lamella and underlying posterior lamella were intact, with no visible exit wound. Rest of the ocular examination was unremarkable except for minimal bulbar conjunctival congestion inthe left eye. The fish hook was removed under local anesthesia by gray line split approach. A 3 mm incision over the gray line on either side of the entry wound was made, and gentle dissection separating orbicularis oculi from the underlying tarsus was carried out up to 4 mm from lid margin thus exposing the barb and the sharp tip of the hook enabling easy removal of the hook [Figure 1b]. The anterior and posterior lamellae were well opposed by direct pressure. The eye was patched with an antibiotic eye ointment. Patient received intramuscular tetanus toxoid injection. He was prescribed nonsteroidal anti-inflammatory drugs for 5 days. The patient was lost to follow up.

DISCUSSION

Commonly used fish hooks have a sharp point and a back-cutting sharp barb. A similar model of fish hook was

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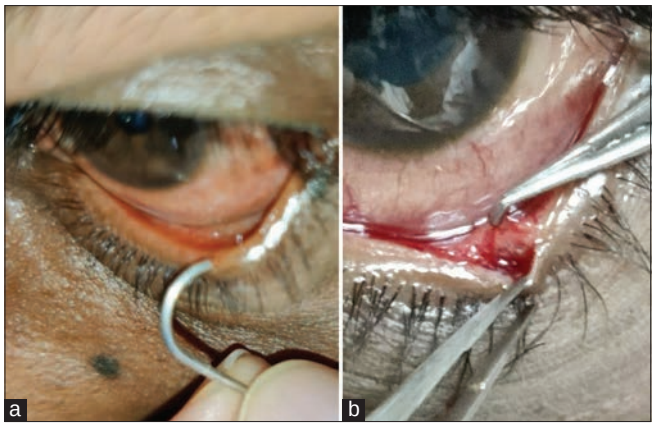


Figure 1: (a) External clinical photograph showing the fish hook entering the patient's left lower eyelid margin at the junction of medial two-third and lateral one-third (b) Showing gray line split technique with anterior and posterior lamellae seen separately after fish hook removal

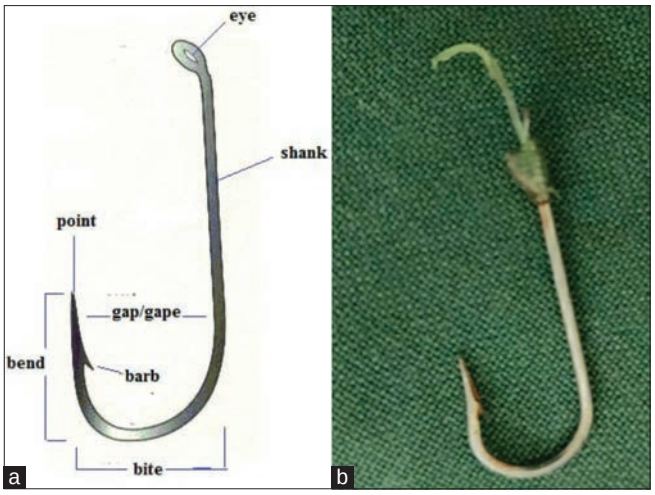


Figure 2: (a) Photograph of various parts of a barbed fish hook (b) Clinical photograph of the fish hook foreign body following its removal

found in our case [Figure 2a and b]. Purtskhvanidze *et al*.[1] in their case series on fish hookrelated ocular injuries reported excellent postoperative outcomes in five out of nine cases. Various techniques of fish hook removal have been described in the literature.[2-4] They include:

1. Back out or retrograde method: This method is used to remove barbless hooks where the hook is pulled backwards through the entry wound. This method can cause further tissue trauma in case of penetrating globe injuries. A modified version of this technique was adopted by Iannetti L *et al*.[5] in his case of penetrating globe injury by fish hook where the entry wound was enlarged before pulling out the hook.
2. Cut it out technique: The entrance wound is enlarged and dissected to expose the barb and sharp tip of the hook as described by Ahmad *et al*.[6] We have adopted a similar technique in our case as well.
3. Snatch or string yank technique: This technique was used for non-ocular fish hook trauma where a downward pressure is applied on the shank of the hook, and the hook is rapidly pulled out. This technique is significantly traumatic to the eye.
4. Advance cut method: This technique is less traumatizing as a second incision is made near the barb of the hook, and the hook is cut between the barb and the bend. The sharp tip along with the barb is then removed through the second incision, and the shank is removed through the entry wound using back out technique.
5. Advance without cut method: This method is similar to "Advance cut method" where the entire hook is advanced through a second incision made near the sharp tip of the hook without cutting the hook in between.
6. Needle cover technique: Described by Grand and Lobes for a fish hook penetrating the globe and the retina,[7] a wide bore needle is passed after enlarging the entry wound. The fish hook barb is then engaged within the lumen of the needle, and both are withdrawn together to deliver the hook out of the eye.

Our case, with a unique presentation adds to the existing literature of wide spectrum of presentation of fish hook–related ocular injury.

CONCLUSION

The choice of surgical technique for fish hook removal is dependent upon various factors such as the site of injury, type of fish hook, and severity of injury. Every attempt should be made to prevent further tissue trauma while attempting removal.

In our case, the "gray line split-cut it out technique" was employed for atraumatic removal of the hook.

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Conflicts of interest

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Case Report

Lacteocrumenasia

ABSTRACT

Capsular bag distension syndrome (CBDS) is a rare complication of cataract surgery characterized by collection of turbid fluid between the posterior surface of the intraocular lens (IOL) and the posterior capsule. Here, we report a case of CBDS presenting 7 years after uneventful cataract surgery. Patient presented with blurring of vision in the right eye and his best corrected visual acuity (BCVA) was 6/9 N6. Slit lamp examination showed collection of turbid fluid between IOL and posterior capsule, and the opaque fibrosed capsulorhexis margin was adherent to the optic of IOL which was well placed within the bag. Patient underwent neodymium yttrium aluminium garnet (ND-YAG) laser posterior capsulotomy to release the fluid into the vitreous cavity. 6 weeks after the procedure his BCVA improved to 6/6 N6.

Keywords: Capsular bag distension syndrome, lacteocrumenasia, neodymium yttrium aluminium garnet laser

INTRODUCTION

Capsular bag distension syndrome (CBDS) is a rare complication of cataract surgery reported in 0.73–1% of patients. Basically this occurs due to adherence of capsulorhexis rim to the optic of intraocular lens (IOL) preventing free flow of fluid through the anterior capsule opening with accumulation of fluid behind the IOL and distension of posterior capsule.

Lacteocrumenasia (liquified after cataract) is a type of CBDS occuring in the late postoperative period. Commonly CBDS presents with unexplained myopia, reduced vision, shallow anterior chamber and occasionally with high intraocular pressure. However these are less common in lacteocrumenasia.

CASE REPORT

A 76-year-old male presented to us with a history of gradual diminution of vision in the right eye of 3 weeks duration, without any other ocular symptoms. He had undergone cataract surgery in right eye 7 years ago and in the left eye 5 years ago in another hospital. Postoperative period was reportedly uneventful. He was diabetic for 15 years. He did not have any other systemic illness. On examination his best corrected visual acuity (BCVA) in the right eye was 6/9, N6 and left eye was 6/6, N6. There was no myopic shift in his refraction in the right eye compared to the previous visit 2 years back.

He was pseudophakic and anterior chamber was quiet in both eyes. IOL was looking normal in left eye but in the right eye the IOL seemed to have an yellowish tinge. Intraocular pressure was within normal limits in both the eyes.

Slit lamp examination after dilatation showed a well-centred single piece IOL in the bag in the left eye. In the right eye the single piece IOL was transparent and was placed well inside the bag. The anterior capsule rim was opacified and fibrosed, and was adherent to the anterior surface of the IOL optic. There was white proliferative tissue inferiorly behind the IOL and yellowish white turbid fluid had accumulated between the posterior surface of IOL and posterior capsule

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[Figure 1a and b]. Dilated fundus examination of the right eye was hazy due to the turbid fluid, but appeared normal. Left eye fundus was normal.

Presence of turbid fluid between the posterior capsule and the posterior surface of IOL and a fibrosed opacified rhexis margin adherent to the optic in this patient years after cataract surgery were features typical of late onset capsular bag distension syndrome (CBDS) or lacteocrumenasia. Patient underwent neodymium yttrium aluminium garnet (ND-YAG) laser capsulotomy and the turbid fluid was released into the vitreous [Figure 2a–c]. Postprocedure he was given topical steroid eye drops (prednisolone acetate 1.0% eye drops 6 times per day for 1 week and 4 times per day for 3 weeks) and topical antiglaucoma medication (timolol maleate 0.5% twice daily for 1 month). He was reviewed at 1, 2, and 6 weeks after the procedure. Through out the follow-ups his IOP was normal. His visual acuity remained same in the initial two follow-ups due to the dispersion of fluid in the anterior vitreous but at 6 weeks his vision improved to 6/6, N6.

DISCUSSION

CBDS is a rare complication of cataract surgery with a reported incidence of <1% among those who have undergone phacoemulsification with posterior chamber IOL implantation.[1] A large retrospective study found that eyes with axial length >25mm, and patients who received 4 Haptic posterior chamber intra ocular lenses (PC-IOLs) had increased risk of CBDS.[2] Retained ophthalmic visco elastic devices, inadequate subincisional cortical cleaning, IOLs with soft haptics and biconvex designs, postoperative inflammation, capsular fibrosis, and smaller capsulorhexis are all known to predispose to this condition.

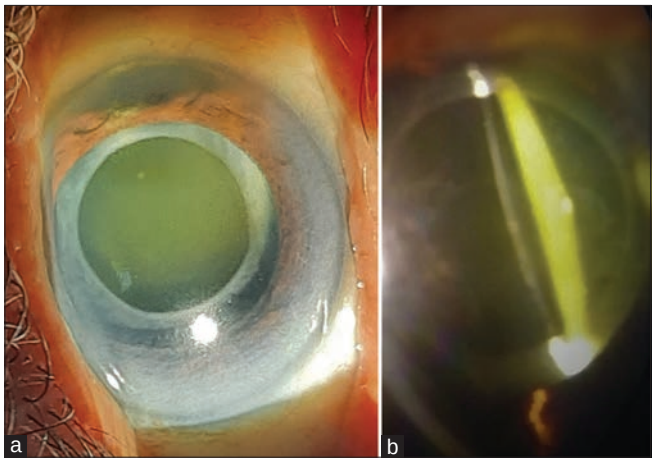


Figure 1: (a and b) Shows the opacified anterior capsule rim adherent to the IOL optic and yellowish turbid fluid between the IOL and the posterior capsule

Based on the onset, Miyake *et al*.[3] has classified CBDS into three types, intraoperative, early postoperative, and late postoperative [Table 1]. Based on the pathology Kim and Shin[2] classified it into fibrotic, inflammatory, and noncellular types [Table 2]. The intraoperative CBDS occurs following rapid hydrodissection with accumulation of fluid behind the nucleus. Early postoperative CBDS presents itself within 1–15 days of cataract surgery, due to viscoelastic substance being trapped between the IOL and the posterior capsule. This often leads to myopic shift in refraction, raised IOP, and shallow anterior chamber owing to anterior displacement of IOL optic. This is the noncellular type in Kim and Shin classification.

Late onset CBDS commonly occurs 3–8 years after cataract surgery, sometimes it has been reported as late as 13 years postsurgery.[2] Here lens epithelial cells proliferate and undergo metaplastic changes and produce collagen and extracellular matrix which accumulate within the capsular bag.[2] Features such as raised IOP, shallow AC, and myopic shift are less common in late onset type due to the fibrosis and adhesion of the capsulorhexis rim to the optic of the IOL which prevents its anterior displacement. This is the fibrotic type of CBDS. This has been substantiated in the studies done by Landa *et al*.[4] and Pinarci *et al*.,[5] where they found a difference of only 0.50D change in refraction posttreatment.

Electrophoresis done on the contents of capsular bag found high amounts α and β crystalline and small amounts of albumin and calcium.[6] The absence of γ globulins in the contents pointed out the fact that there is no role for immunological

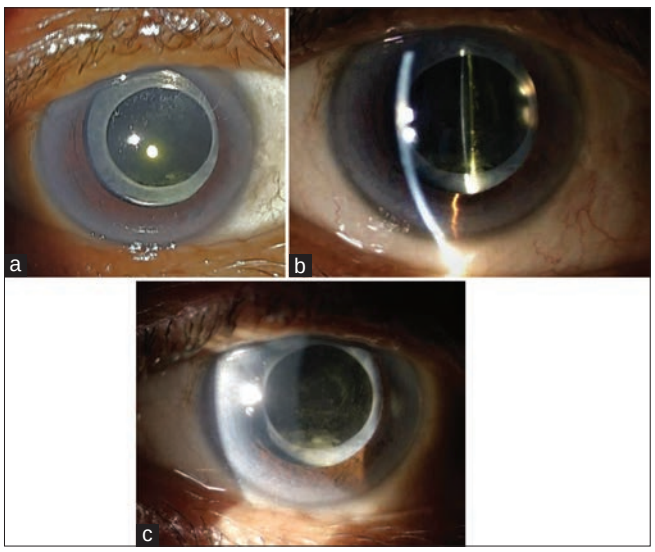


Figure 2: (a-c) Shows the transparent IOL, disappearance of yellowish turbid fluid, posterior capsule opening and the whitish proliferation inferiorly behind the IOL

Table 1: Classification according to time of development of CBDS

Chronologic classification of capsular block	Intraoperatory	Early postoperatory	Late postoperatory
Time of development	Intraoperatory	1-15 days after surgery	3.8 years after surgery
Causes	Rapid hydrodissection, using high amounts of balanced solution	Unknown	Pseudo-metaplasia of lens epithelial cells?
Related anomalies	Ocular axial length posterior polar cataract	–	Breach in blood–aqueous barrier?
Blocking substance	Cataract nucleus	Iol optic	Iol optic
Accumulated substance	Balanced solution	Transparent viscoelastic	Whitish liquid
Shallow anterior chamber	Yes	Yes or no	Yes
IOP increase	No	Yes or no	Yes
Refractive change	–	Myopic shift	No
Complications	Posterior capsule rupture	Closed angle glaucoma	Visual acuity decline (fairly rare)
Treatment	Posterior vitrectomy	Nd: yag laser	Nd: yag laser
Prophylaxis	Careful hydrodissection	Removal of intraoperative viscoelastic	Removal of residual cells

Miyake K, Ota I, Ichihashi S et al. New classification of capsular block syndrome

Table 2: Pathophysiological classification

Parameter	Fibrotic	Inflammatory	Non-cellular
Expected main cause	Lens epithelial cell proliferation and pseudometaplasia	Inflammatory anterior chamber cellular reaction	Remaining OVD
Time of onset	Late postoperative period (several months to years after surgery)	Early postoperative period (several days after surgery)	Very early postoperative period (from one to several days after surgery)
Treatment	Disruption of capsular bag	Anti-inflammatory drugs	Disruption of capsular bag or aspiration of retained OVDs

Kim HK, Shin JP, Capsular block syndrome after cataract surgery: clinical analysis and classification

mechanism in the pathogenesis of CBDS. Isolated case reports revealed a possible role for propionibacterium acne.[7] The diagnosis of CBDS is clinical, however anterior segment OCT, ultrasound biomicroscopy, and schiempflug imaging help in diagnosing and visualizing the pathology.

The widely used treatment approach for CBDS is posterior capsulotomy with ND-YAG laser. This creates a path to disperse the contents into vitreous cavity, resulting in improvement in visual acuity. It has minimal collateral effects, low complication rates, and is relatively less expensive. Other treatment options include anterior capsulotomy especially if the opening is small and fibrosed and slit lamp or pars plana needling. The fluid, cortical material, and opacified posterior capsule can also be removed surgically through the anterior or posterior approach.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

A missing lens-congenital aphakia?

ABSTRACT

Congenital aphakia (CA) is a rare disease of the absence of the lens since birth. It may be primary or secondary. Primary aphakia is due to the failure of induction of surface ectoderm to form the lens. It is often associated with ocular maldevelopment. The disappearance of a developed lens by reabsorption or extrusion results in secondary aphakia. A 27-year-old, male patient presented with diminished vision in the left eye since birth, no history of *in-utero* infection, trauma. On ocular examination, the right eye was normal. The left eye had 30 exotropia; vision was 1/60 with microcornea, corneal opacity, corneal thinning, aphakia, and disc coloboma. B scan revealed posterior staphyloma and aphakia. Congenital Aphakia with associated ocular maldevelopment is a rare case of congenital primary aphakia. It requires a meticulous evaluation and high suspicion to diagnose such a case at birth and follow a multimodal approach to avoid amblyopia and ocular morbidity.

Keywords: Coloboma, Congenital aphakia, microcornea

INTRODUCTION

Congenital aphakia (CA) means the absence of lens since birth. It may present along with abnormal ocular structures along with the absence of lens. It being a rare condition its prevalence is unknown. The often observed abnormal maldevelopments include microphthalmia, corneal thinning, anterior segment dysgenesis, colobomas. The disappearance of a lens following development secondary to trauma, extrusion, or absorption, leads to secondary congenital aphakia. In our case, the patient presents with aphakia along with anterior and posterior segment maldevelopment. No trauma, congenital infection, family history makes it a unique presentation.

CASE REPORT

A 27-year-old male patient presented to us with complaints of diminished vision in the left eye since birth. It was associated with whitish discoloration of his left eye since birth. The child was born out of nonconsanguineous marriage, following an uneventful full-term pregnancy. Delivery was by cesarean section, with no history of assisted delivery/birth trauma.

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Parents noted the abnormal appearance of the left eye compared to the right and consulted an ophthalmologist. Ocular surgery was advised. The patient was lost to follow up and no intervention was done. At 6 years of age, the patient revisited the ophthalmologist and was advised occlusion therapy, which was attempted, however, no visual improvement was observed, following which poor visual prognosis was explained. Following that patient presented to us 11 years later.

There was no similar history in family members. Systemic illness was nil.

Ocular examination

Right eye: visual acuity was 6/6. The anterior segment, fundus examination, and extraocular movements were normal in

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the right eye. Left eye [Figure 1: Showing left exotropia with perilimbal thinning of the left eye, source-original]: Exotropia of approximately 30°. Visual acuity was 1/60, cornea measured vertically 9 mm and horizontally 9.5 mm, had inferior thinning, diffuse macular grade opacity inferiorly 7 mm × 3 mm, with diffuse stromal haze involving rest of the cornea [Figure 2: Left eye corneal opacity inferiorly, approximately 3 mm in height from the inferior limbus and a length of 7 mm (red arrow, source-original).

Sclera

Thinning was noted in the nasal perilimbal area extending up to 2 mm nasally from the limbus. The anterior chamber was deep and optically clear. Iris: Iridodonesis was noted.

Pupil was 3 mm, reacting to light. The pupillary area was jet black, with a tag of a transparent membrane between 12 and 1-clock hours. [Figure 3: Optical section of the left eye showing a jet black pupil with a tag of the transparent membrane (red arrow) between 12 and 1 o clock position, source-origina]. Lens: Aphakia.

Fundus of the left eye

Grossly visualized, coloboma involving disc, other details could not be made out due to nondilating pupil (4 mm) and hazy media.

Squint evaluation revealed 30°exotropia with left suppression with corneal opacity with aphakia.

Investigation

B scan: Left eye: Absence of lens, posterior staphyloma.

DISCUSSION

Aphakia – literally meaning A-phakos, i.e., without the crystalline lens. It may congenital or acquired in nature following surgery or trauma.[1]

Congenital aphakia is extremely rare disease. It may be primary or secondary congenital aphakia. Primary congenital aphakia is related to genetic mutations involving PAX 6 and FOXE3 genes.[2,3] A role of *in utero* infection with rubella and other viruses have also been implicated in primary congenital aphakia.[2] It often presents with the absence of lens associated with abnormal development of eye involving anterior and posterior segment structures.[2] Associated findings include microphthalmos, nystagmus, thinned-out cornea, maldeveloped iris, ciliary body, trabecular meshwork, retinal dysplasia, choroidal and disc colobomas.[1-3]

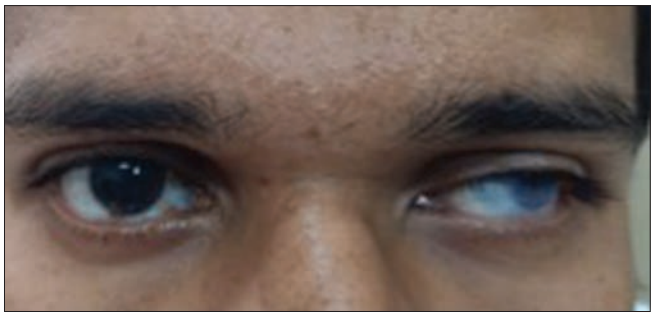


Figure 1: Left exotropia with perilimbal thinning of the left eye, source-original

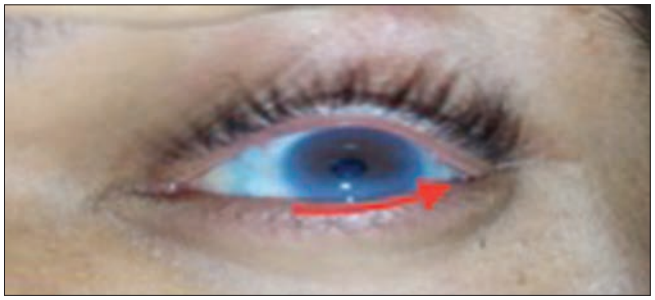


Figure 2: Left eye corneal opacity inferiorly, approximately 3 mm in height from the inferior limbus and a length of 7 mm (red arrow, source-original)

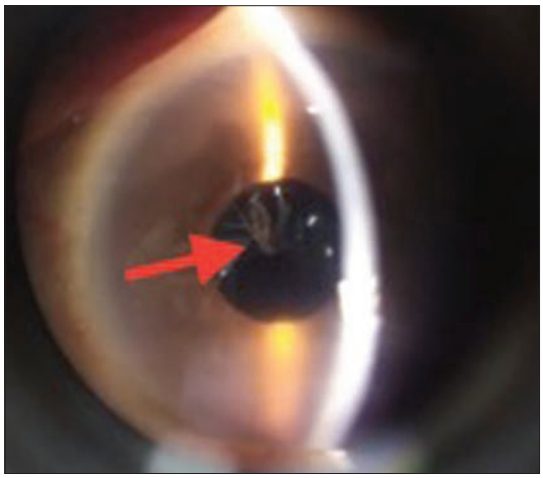


Figure 3: Optical section of the left eye showing a jet black pupil with a tag of the transparent membrane (red arrow) between 12 and 1 o clock position, source-original

Secondary congenital aphakia: arises due to partial or complete disappearance of the developed lens by absorption or by extrusion, probably the following trauma.[1]

Summary

Our case is one of Congenital Aphakia, in the left eye with sensory exotropia 30 and amblyopia. He has associated microcornea, with corneal thinning with optic disc coloboma.

The above-mentioned findings with a combined involvement of anterior and posterior segment in the eye, with a history devoid

of *in utero* infection, no birth trauma is more in favor of the primary congenital variant. Confirmation of the disease is usually genetic studies. Management is multimodal with the primary goal being the correction of aphakia and preventing amblyopia. However, the late presentation in our case, led to amblyopia making vocational rehabilitation the main role of our treatment.

CONCLUSION

This case shows that congenital aphakia although very rare, may present, even in isolation and requires a highly vigilant eye to clinch the diagnosis. It requires a meticulous examination to detect the associated ocular maldevelopments and prompt multimodal management of every component to prevent avoidable ocular morbidity.

Although higher diagnostic methods of genetic evaluation may be required to confirm of a case, a thorough ocular evaluation with the basic diagnostic tools will allow diagnosis and management of a case and improve the quality of life for the patient.

Declaration of patient consent

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

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

A case of eyelid avulsion injury caused by bull horn

ABSTRACT

An 18-year-old male presented with a history of injury to the right eye with a bull horn. Examination revealed an avulsed flap of the right upper eyelid from medial canthus up to 1 cm above lateral canthus without any other ocular damage. After a thorough examination, the lid flap was sutured in layers. Postoperative antibiotic prophylaxis was given. The postoperative complication was in the form of mechanical ptosis.

Keywords: Avulsion injury, bull horn, eyelid

INTRODUCTION

Bull or cow horn injuries are common among people dealing with animals and can cause serious injuries by their various appendages, especially horns. Bull horn injuries to the head or face can be in the form of lacerations, fractures, palate injuries, blow out fracture of orbit, and eyeball injuries.[1] The majority of the cow horn injuries studied caused severe permanent impairment of vision. Owing to the blunt nature of the horns, a significant amount of energy is imparted into the eye.[2] The literature search did not reveal many cases of bull horn injury causing only avulsion of the eyelid without affection of any other ocular structures, and hence, we report this interesting case.

CASE REPORT

An 18-year-old patient presented to the casualty of tertiary care center with a 2-h history of being hit by a bull horn in the right eye. There was no history of sudden diminution of vision following trauma.

Examination revealed an avulsed flap of the right upper eyelid extending from medial canthus up to 1 cm above lateral canthus [Figure 1]. The levator palpebrae superioris muscle was unaffected; however, its action could not be demonstrated due to mechanical ptosis as a result of eyelid edema. The rest of the anterior segment appeared normal with best-corrected visual acuity of 6/6 by Snellen's chart. The posterior segment appeared normal by indirect ophthalmoscopy.

Avulsed eyelid flap was sutured under local anesthesia after thorough wound cleaning with normal saline and 5% povidone-iodine solution. The lid flap was sutured in layers using 6-0 Vicryl suture [Figure 2]. The patient was vaccinated with 0.5 ml tetanus toxoid and was prescribed topical moxifloxacin eye drops 4 times per day and systemic antibiotics-amoxicillin-clavulanic acid 625 mg and T. Metronidazole 400 mg for 1 week. Mechanical ptosis of the right upper eyelid was noticed at the first follow-up visit.

DISCUSSION

Bull horn injuries are common accidents in rural India, where people make their living rearing the livestock for domestic and farming purposes. The patterns of injuries sustained by

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Figure 1: Right upper eyelid flap avulsed from medial canthus up to 1 cm above lateral canthus without any other ocular damage



Figure 2: Postoperative image of the right upper eyelid sutured with 6-0 Vicryl suture

the victim depend on the height of the victim, height of the bull, position of the animal, and victim at the time of the attack.[3]

Most of these injuries due to bull involve the lower extremities, whereas those involving the face and neck are very less.

The injuries produced by bull goring can be classified into blunt wounds, or contusions, and penetrating or open wounds.

To these injuries must be added the fractures that generally result from the charge of the bull. Burns may occur when the bull has flares or torches attached to its horns.[4]

Eyelid avulsion due to bull horn injury as a sole finding is extremely rare. It is usually the result of the blunt tangential impact on the side of the horn that leads to horizontal traction on the eyelid which causes avulsion at a weak point, usually at the medial or lateral canthal tendon. However, sometimes, avulsions starting from other areas can occur.[5]

For full-thickness upper eyelid injuries, never forget to check for globe perforations. Globe injuries should be attended before lid injuries. Eyelid trauma can be associated with hyphema, angle recession, or retinal detachment. Clear watery discharge from one nostril indicates cerebrospinal fluid rhinorrhea and is a red alert sign to look for anterior skull base fractures.

All eyelid tissues should be saved, as high vascularity often allows for viable re-approximation of partially avulsed ocular adnexal tissue.[6] If the canalicular damage is found, repair by stenting should be undertaken before the repair of the avulsed lid flap.[7]

The general management of these patients must include:

- Preoperative and postoperative antibiotic therapy and tetanus vaccination
- Wounds must be cleaned exhaustively with saline solution and an antiseptic solution (hydrogen peroxide and/or povidone-iodine) and all foreign bodies (horn splinters, stones, dirt, and remains of clothing, glass, and others) must be removed.[8]

CONCLUSION

Reconstruction of the eyelid should be done in layers as per correct anatomical orientation. Full-thickness lid margin lacerations, canalicular tears, canthal injuries, and lacerations with tissue loss are entities which should be meticulously tackled using specialized techniques.[6]

Declaration of patient consent

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Case Report

A case report of eyelid pilomatrixoma: A rare presentation

ABSTRACT

Pilomatrixoma is a rare periocular benign tumor involving hair follicle matrix cells. It presents as a hard, painless, and gradually enlarging mass. It is more common in Caucasians, has bimodal age distribution (5–15 years and 50–65 years) and with female preponderance. We present a rare case report of a 35-year-old Indian male presenting with progressively enlarging; noninflammatory mass in the left upper eyelid for which excision biopsy was performed and a diagnosis of pilomatrixoma was arrived at. The main differential diagnosis includes chalazion and it is vital to distinguish them prior to any surgical intervention as both have different lines of management. This article also deals with the clinical as well as histopathological features and syndromic association of pilomatrixoma along with a brief mention of its malignant variation. This case report also includes intraoperative photographs of the lesion which the authors could not find during literature search.

Keywords: Chalazion, eyelid mass, pilomatrixoma

INTRODUCTION

A pilomatrixoma, also known as calcifying epithelioma of Malherbe, is a benign appendageal tumor with differentiation toward hair follicle matrix cells.[1]

CASE REPORT

A 35-year-old male, computer operator by occupation, presented with a complaint of gradually increasing painless swelling in the left upper eyelid for 2 months. The history revealed the absence of redness around the lesion or in the eye during the entire period of progression. The patient had no history of trauma or systemic illness. There was no history of similar complaint in the family. The swelling was diagnosed as chalazion at first presentation and warm compresses, lid massage, and topical medication were advised. In spite of patient being compliant, swelling did not regress and he presented again after a month with an enlarged size.

On inspection, a single large mass with well-defined margins involving the left upper eyelid causing mechanical ptosis was observed. The eyelid margin was uninvolved and overlying skin showed reddish-blue discoloration [Figure 1]. On palpation, the mass was found to be around 9 mm × 5 mm size, nontender, hard in consistency, and located on pretarsal area, which could be moved over underlying structures. The overlying skin was adherent to the mass. On eyelid eversion, palpebral conjunctiva appeared normal. The uncorrected visual acuity was 20/20 and the rest of other ocular examination was unremarkable. Examination of the right eye was within normal limits. Systemic examination did not reveal any lymphadenopathy or nodular lesion elsewhere.

In view of the mass increasing in spite of medical treatment, excisional biopsy was planned. Routine blood investigations were normal and the patient was taken to operating room.

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Local infiltration with 2% lignocaine followed by painting and draping was performed. Mass was approached from the skin side. Under microscope, a horizontal circumlinear skin incision was given along the superior border of the mass followed by meticulous dissection of surrounding adhesions. Single, isolated, and encapsulated nodule was excised without rupturing its wall. No hemorrhagic or ulcerative patterns were noted in the adjacent tissues. The root of follicles could be visualized in close proximity of the nodule [Figure 2]. Wound was closed by applying interrupted (8-0) Vicryl sutures. Excised sample was sent *en bloc* for histopathological (h/p) analysis in a vial containing 10% formalin. There were no intraoperative or postoperative complications. Routine postoperative medications were administered.

On H/P: Grossly, a single, globular pinkishbrown encapsulated mass with smooth outer surface measuring 6 mm × 3 mm × 2 mm was seen. Whole sample was processed and embedded in one block. Multiple sections of 5 µ each were cut and stained by Hematoxylin and Eosin stain, following which they were examined under microscope at ×10 and ×40 magnification.

Under microscope, the tumor showed sheets of bland, uniform, and basophilic hair matrix cells. Large masses of ghost/shadow cells, basaloid cells, and inflammatory cells were observed. Confluent foci of dystrophic calcification of the matrix with keratin were seen. Ghost cells are suggestive but not pathognomonic of pilomatrixoma and represent necrotic areas of previously vital basaloid cells. Careful serial sections did not show malignant change in any field of the lesion. Based on these features, a histopathological diagnosis of a pilomatrixoma was arrived at.

DISCUSSION

Pilomatrixoma (pilomatricoma), a benign tumor of the hair follicle, was first described by Malherb in 1880 as "calcifying epithelioma" and was thought to be derived from the sebaceous gland. Later on, in 1949 Lever and Griesemer suggested the hair matrix cells to be the origin of the tumor and finally in 1961 Forbis and Helwig proposed the currently accepted name "pilomatrixoma."

Pilomatrixoma while commonly encountered in other parts of the body is a rare periocular tumor. The most common periocular location is the eyebrow but can involve the eyelid. There are limited reports in the literature on eyelid pilomatrixomas.[2,3]

The age of presentation shows a bimodal pattern, with the first peak being 5–15 years and the second being 50–65 years with a female preponderance. A racial study revealed that most cases are presented in Caucasians and relatively few in Asians.[4]

Isolated pilomatrixomas are non-hereditary type. Mutations in the exon 3 of the CTNNB1 gene, located on chromosome 3p22-p21.3, which encodes the beta-catenin protein implicate beta-catenin as the major cause of hair-matrix cell tumorigenesis. Multiple pilomatrixomas are familial type, associated with Steinert's myotonic dystrophy, Gardner Syndrome, Turner Syndrome, Trisomy 9, Rubinstein-Taybi syndrome, Xeroderma-pigmentosum, etc.[5,6]



Figure 1: Clockwise from top to left: Torch-light photograph of the left upper eyelid swelling with mechanical ptosis; Slit-lamp photograph depicting reddish blue discoloration of overlying skin due to dilated blood vessels; Photograph after lid eversion showing un-involved upper tarsal conjunctiva; postoperative 1 month photograph showing reversal of ptosis after excisional biopsy

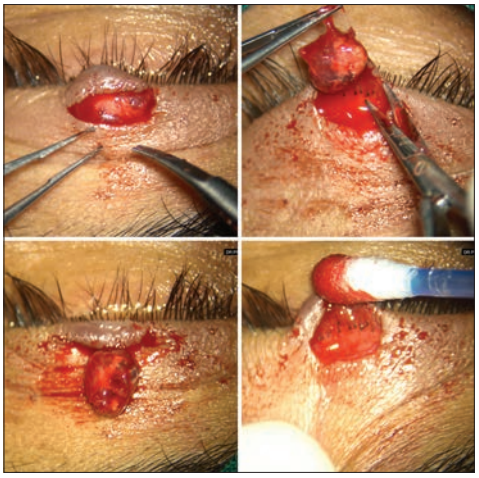


Figure 2: Intraoperative photographs: clockwise from top to left: exposed subcutaneous mass after horizontal skin incision; encapsulated mass being delineated after surrounding adhesiolysis; completely excised nodule; hair follicles underneath the excised nodule, adding to the diagnosis

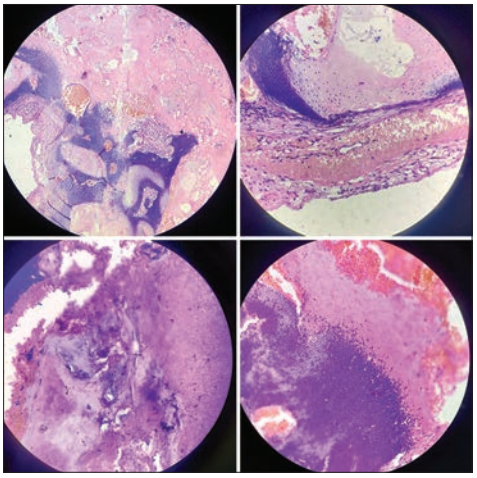


Figure 3: Photomicrographs at ×40 (clockwise from top left): Abruptly keratinized ghost cells with mild calcification; overlying epithelium with increased subepithelial vascularity; Solid nests of basaloid cells undergoing abrupt trichilemmal type keratinization; calcification seen in ghost cells

Our patient was a 35-year-old Asian male, with no familial history or syndromic association, and the mass was located in the eyelid. Hence, portraying is a rare presentation of pilomatrixoma.

Clinically, the lesion appears as a slowly enlarging, irregularly shaped, hard, nodular, and nontender mass freely movable over the subcutaneous tissue, but not under the skin. The skin usually has reddishblue discoloration due to dilated blood vessels and chalky white nodules may be seen through the skin. Usually, there is no history of inflammation or trauma.[3] The distribution of pilomatrixoma depends on the density of pilosebaceous glands in a given area.[7]

Pilomatrix carcinomas can occur but are uncommon, they are locally invasive and can cause visceral metastases and death. It occurs more often in middle age or older individuals, more commonly in men than in women. Microscopically, it is characterized by exuberant proliferation of basaloid cell masses with varying degrees of cytological atypia, frequent mitoses, and areas of necrosis. The keratinization with shadow cell formation is less extensive than in benign pilomatrixoma. The infiltrative growth pattern which extends into deeper soft tissues may display vascular and perineural invasion. No such features suggestive of carcinomatous changes were noted clinically or histopathologically in our patient [Figure 3].

Differential diagnoses of pilomatrixoma include epidermal inclusion cyst, sebaceous adenoma, dermoid cyst, epidermoid cyst, and vascular tumors such as capillary hemangioma. These tumors have similar clinical appearance, making histopathological analysis mandatory.[3]

CONCLUSION

Pilomatrixoma is a benign condition often masquerading as chalazion. A 35-year-old man presenting with gradually enlarging, hard, painless swelling on the left upper eyelid underwent excision biopsy which later-on confirmed as pilomatrixoma. The mainstay of treatment involves complete surgical excision.

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Declaration of patient consent

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Nil.

Conflicts of interest

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Case Report

External ophthalmomyiasis: Slither sign in orb

ABSTRACT

Ophthalmomyiasis is the myiasis of the eye, a relatively rare condition characterized by infestation of ocular and orbital tissues with fly larvae. Oestrus ovis being the most common causative organism. It typically occurs in shepherds and farmers in rural areas. The clinical symptoms depend on the extent of tissue invasion, which may include conjunctivitis, haemorrhage or ulceration. We report a case of 20 y/M who presented to us with foreign body sensation and watering in right eye since morning, and redness since 1 day. His visual acuity in right eye was 6/9 and in left eye was 6/6. On slit lamp examination, anterior segment of right eye revealed lid oedema, mucopurulent discharge, papillae, conjunctival congestion and moving larvae about 15-20 in number were seen on cornea and conjunctiva. Rest was unremarkable. Causative larvae were removed with forceps under topical anaesthesia followed by instillation of antibiotic eyedrop. The causative larvae were sent for microbiological examination and were identified as the first stage larvae of Oestrus ovis, the sheep nasal bot fly. Very few cases of external ophthalmomyiasis have been reported from urban areas of Maharashtra in India.

Keywords: External ophthalmomyiais, *Oestrus ovis*, urban area

INTRODUCTION

Ophthalmomyiasis, a rare ailment, is the myiasis of the eye, marked by fly larvae infestation of ocular and orbital tissues. Conducive organisms include *Oestrus ovis, Calliphora*, *Sarcophaga*, *Lucilla,* etc. Most commonly, *O. ovis* is the causative organism of ophthalmomyiasis. It can occur in three forms: external (larvae deposited on the ocular surface), internal (larvae penetrates the globe), and orbital (reaches orbital structures).[1] Orbital ophthalmomyiasis is the most damaging type.

It is predominantly seen in rural areas, in shepherds, and farmers. Predisposing factors include ocular infections, ocular injuries, old age, debilitation, and poor general health. The clinical features depend on the level of tissue invasion, which includes conjunctivitis, hemorrhage, and ulceration. It may cause blindness rarely.[2] Many countries including Afghanistan, Pakistan, the Caribbean, Kuwait, Iraq, The United States, Canada Libya, Tunisia, Russia, and India have reported cases of ophthalmomyiasis. In India, cases have been reported from Allahabad, Tamil Nadu, Western UP, and North India; Eliot reported the first case in India.[3]

Here, we report a case of external ophthalmomyiasis, causative organism being *O. ovis* at a tertiary care center in an urban area.

CASE REPORT

A 20 years old male presented to ophthalmology outpatient department (OPD) with chief complaint of foreign-body sensation and watering in the right eye since morning and

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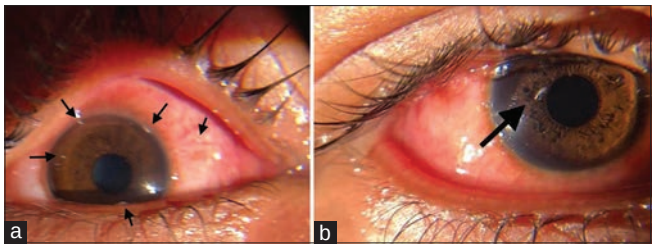


Figure 1: (a) and (b) showing presence of larvae seen on cornea and conjunctiva in the right eye

redness since the previous night. He also complained of something going into the right eye while sitting beneath the tree the previous night followed by which he started experiencing the above symptoms. There was no history of ocular trauma, procedure, and systemic illness.

His visual acuity in the right eye was 6/9 and in the left eye was 6/6. On slit-lamp examination, anterior segment of the right eye revealed lid edema, mucopurulent discharge, papillae, conjunctival congestion, and moving larvae about 15–20 in number and 2–3 mm in size were seen [Figure 1a and b]. The rest was unremarkable. Fundus was within normal limits. In the left eye, both anterior and posterior segment was normal.

Topical anesthetic drop was instilled in the right eye, and the causative larvae were removed with forceps, followed by instillation of antibiotic drop.

The causative larvae were sent for microbiological examination. On macroscopic examination, the worms were milky white maggots of about 2 mm in size. Microscopy revealed spindle-shaped skeleton with multiple segments. A pair of sharp, dark brown oral hooks was attached to the internal cephalopharyngeal skeleton, and tufts of numerous brown hooks were on the margins of each body segment. They were identified as the first stage larvae of *O. ovis*, the sheep nasal bot fly [Figure 2].

The patient was advised to apply eye ointment Azithromycin twice a day, eye drop carboxymethylcellulose eight times, and eye drop moxifloxacin 0.5% six times topically in the right eye. On follow-up next day, he was symptomatically better. There was no evidence of larvae, only papillae and mild congestion was seen. He was advised to continue the same treatment and follow-up after 1 week. The patient was referred to ENT OPD, and there was no evidence of the presence of parasites in the nasal cavity. On follow-up after 1 week, the symptoms subsided, and the vision in the right eye improved to 6/6.

Anterior segment and fundus examination of both the eyes were within normal limits.



Figure 2: showing microscopic picture of Oestrus ovis

DISCUSSION

Ophthalmomyiasis is a relatively rare condition characterized by infestation of orbital and ocular tissues with fly larvae. It is uncommon in developed countries but is common in underdeveloped area of the world due to poor standard of living and poor hygiene.

It can occur in three forms: external ophthalmomyiasis, in which larvae are deposited on the ocular surface, internal ophthalmomyiasis, in which larvae penetrate the globe, and orbital ophthalmomyiasis, in which the larvae reach orbital structures and cause damage.[1] Orbital ophthalmomyiasis is the most serious type.

Several offending species have been identified including the human botfly (*Dermatobia hominis*), latrine fly (Fannia), house fly (*Musca domestica*), and cattle botfly (*Hypoderma*), but *O. ovis*, or the sheep botfly, is the most common cause of human ophthalmomyiasis. Natural hosts of the fly *O. ovis* are animals such as sheep, cattle, deer, horse, and rodents and accidental host is humans. The female *O. Ovis* retains her eggs within her body until they hatch, and then typically deposit her larvae into the nostrils of sheep and goats. When they occur in the human eye, larval infections are usually restricted to the conjunctiva and cornea. *O. ovis* infections have also been reported in the human nose and pharynx. In human host, *O. ovis* larvae can survive only up to 10 days.

The clinical course of ocular myiasis is still inconclusive. Severity of clinical features varies from mild irritation to complete orbit destruction.[4] External ophthalmomyiasis is rarely seen in humans. Internal ophthalmomyiasis is less common worldwide than external ophthalmomyiasis, wherein the larvae enter vitreous and may reach subretinal

fluid. OCT imaging through the tracks has reportedly revealed subretinal tunnels.[1]

Social history is essential in the evaluation of ophthalmomyiasis, as the patient may have a recent history of close contact with sheep or goats.

In cases of external ophthalmomyiasis, the patient may report a history of sudden onset of pain, burning, itching, watering, foreign-body sensation, swelling, etc., Slit-lamp examination may reveal small translucent larvae up to 5 mm in length on the conjunctiva. The patient may develop mucopurulent conjunctivitis, or rarely, corneal ulcer or keratitis. Most cases reported are of catarrhal conjunctivitis in the literature. A rare association of *O. ovis* ophthalmomyiasis with keratitis has been reported.[4] Therefore, it is an important differential diagnosis of acute conjunctivitis. Some organisms can penetrate into the eye such as *D. hominis, Hypoderma bovis,* and rarely *O. ovis*. Therefore, urgent removal and identification of the causative organism is necessary.[5] Management includes mechanical removal of larvae using forceps or cotton swab under local anesthesia and instillation of topical antibiotics and lubricants.

To the best of my knowledge, external ophthalmomyiasis is rarely reported from urban areas of Maharashtra.

CONCLUSION

External ophthalmomyiasis is a relatively rare condition in urban areas. Based on its pathology and clinical course, immediate removal of causative organism is essential to prevent complications such as internal ophthalmomyiasis with potential visual consequences.

Declaration of patient consent

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Conflicts of interest

There are no conflicts of interest.

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"Egg in the eye appearance" of traumatic pre-existing posterior capsular defect presenting as near-total cataract

A 10-year-old girl was brought by her parents with complaints of a sudden drop in vision in the left eye (LE) with the appearance of a white reflex for a 1-month duration. There was a history of needle stick injury to the LE 5 years ago which was conservatively managed elsewhere. Previously, she had a vision of 6/9, N6 LE, with glasses as per her old records. The best corrected visual acuity (BCVA) was 6/6, N6 right eye (RE), hand motion (HM), and <N36 LE at the time of presentation. There was a small corneal scar at the 3 o'clock position in the peripheral cornea of the LE. Dilated examination of LE revealed near-total cataract, an intact anterior lens capsule, and a large elliptical area of pre-existing posterior capsular defect (PPCD) resembling an "egg in the eye appearance" [Figure 1]. Ultrasonography (USG) B scan of the LE showed the characteristic "fishtail sign" and confirmed the herniation of the lens matter through posterior capsular dehiscence into the anterior vitreous cavity [Figures 2 and 3] with an intact retina.

The patient underwent a careful continuous curvilinear capsulorhexis (CCC), bimanual irrigation–aspiration of the lens matter, and anterior vitrectomy with reduced parameters of low bottle height, low irrigation, and aspiration, taking care to avoid hydro-dissection and shallowing of the anterior chamber. Intra-operatively, the large posterior capsular dehiscence [Figure 4] was carefully evaluated and cleared off any vitreous incarceration. A foldable three-piece intraocular lens (IOL) was implanted in the ciliary sulcus [Figure 5]. Post-operatively, the patient did well and regained 6/6, N6 vision in the LE, and remained the same until the last follow-up after 1 year [Figure 6].

DISCUSSION

The history of past needle stick injury in our patient with sudden transformation into near mature cataract later points toward the presence of a PPCD which gradually caused microleakage and rapid maturation of the cataract. A dilated examination using a slit lamp and under an operating microscope helped to identify the thick, well-demarcated, elliptical borders of the PPCD, through the near-total cataract simulating an "egg in the eye" appearance. The thickened and fibrosed margins of the PPCD have been attributed to the migration of the hyperplastic epithelial cells to this region.[1] USG B scan confirmed the PPCD with lenticular matter hanging in the vitreous cavity (fishtail sign).[2] Other clinical signs which have been described in the literature include white demarcation lines and white crystalline particles floating in the vitreous, but they may not be evident in all white cataracts with PPCDs.[2] A relatively smaller CCC, closed-chamber bimanual irrigation–aspiration with reduced parameters (low bottle height, irrigation, and aspiration), avoiding hydro-dissection and shallowing of AC, controlled

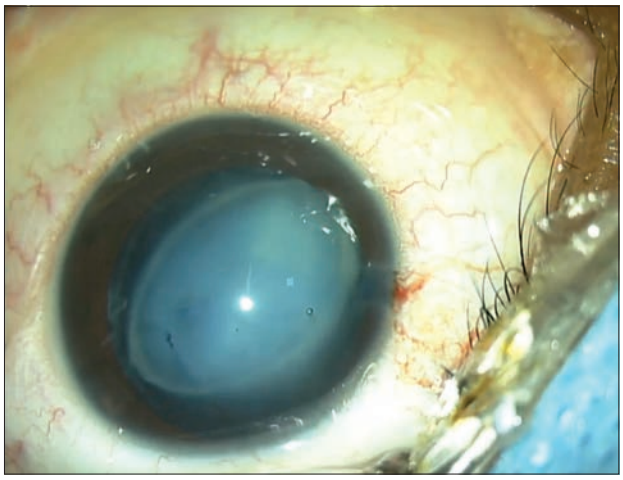


Figure 1: Intra-operative picture of the LE taken after nicking the anterior capsule showing the fibrosed edges of the large elliptical posterior capsular dehiscence

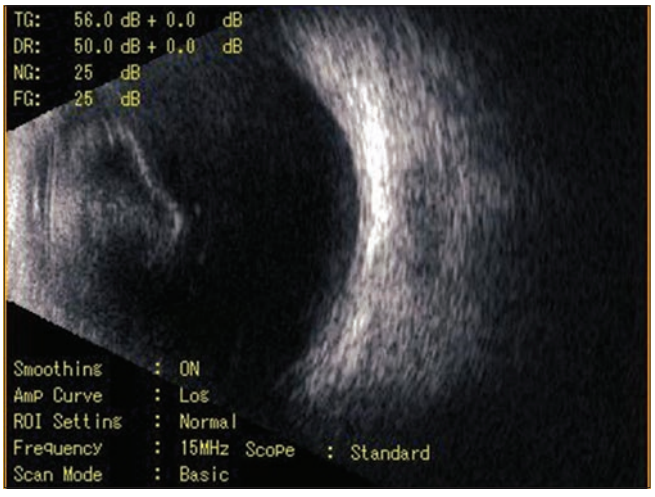


Figure 2: Ultrasound B scan of the LE showing conical protrusion of the breached posterior lens capsule

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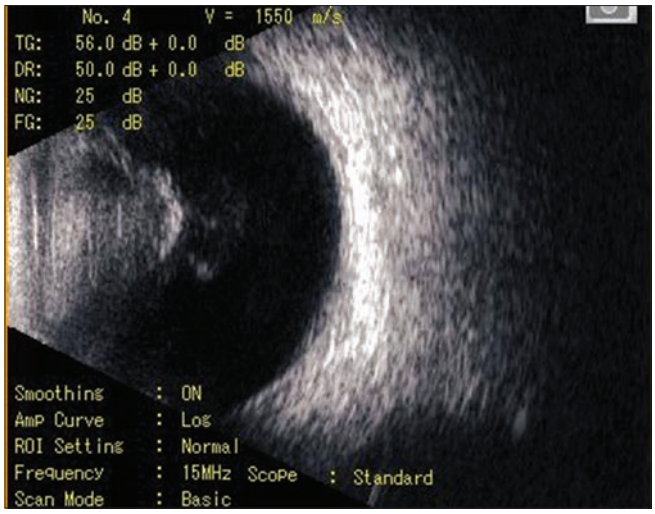


Figure 3: Ultrasound B scan of the LE showing "fishtail sign" with herniation of the lens matter into the anterior vitreous cavity through the posterior capsular dehiscence

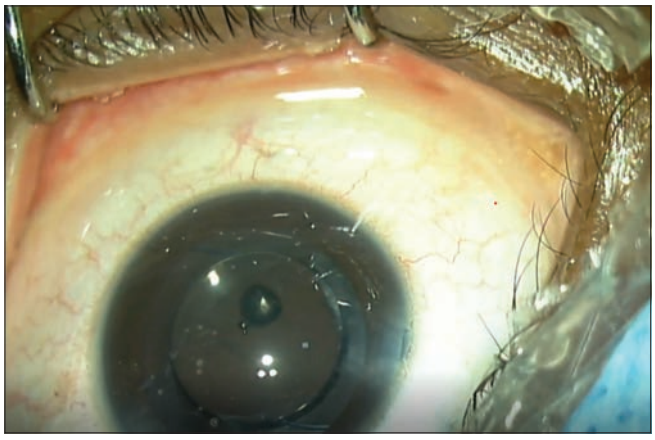


Figure 5: Intra-operative picture after intraocular lens implantation into the LE

anterior vitrectomy, and switching between the cut and aspiration modes to remove the prolapsed lens matter and vitreous are essential to ensure a clear visual axis and safe IOL implantation.[2]

CLINICAL SIGNIFICANCE

All total cataracts are not the same, and surgery without a thorough history, careful examination, and proper planning could be catastrophic to the patient. Surgical management in pediatric cataracts with PPCD remains a challenge due to the increased risk of lens matter drop in the vitreous cavity. Identifying the PPCD, explaining the potential risks to the patient, and taking adequate precautions to avoid lens matter drop are vital steps to a successful outcome.

Acknowledgements

The patient and her parents are acknowledged.

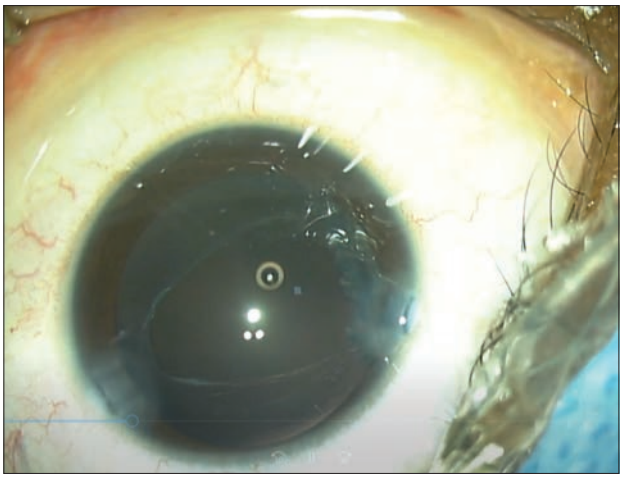


Figure 4: Intra-operative picture of the LE showing the large elliptical posterior capsular defect after lens aspiration

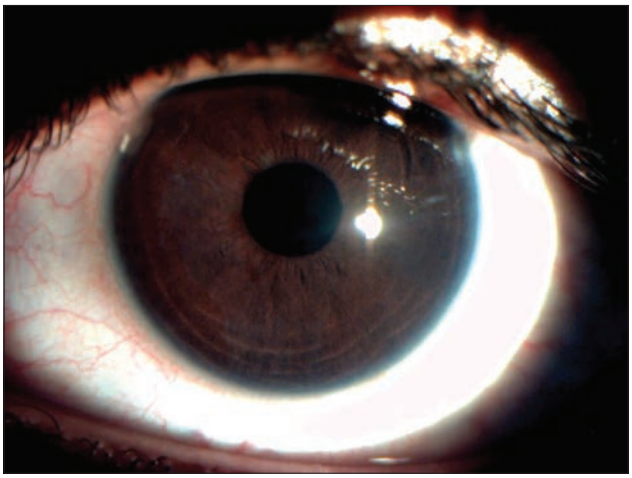


Figure 6: Clear visual axis on follow-up after 1 year

Declaration of patient consent

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Photo Essay

Phthiriasis palpebrarum - An easily missed diagnosis

ABSTRACT

We report a case of phthiriasis palpebrarum, which was previously misdiagnosed as anterior blepharitis. Several lice and multiple nits were noted on the eyelashes in left eye under slit-lamp examination. The patient was successfully managed by mechanical removal of lice and nits after applying 20% fluorescein dye and subsequent treatment with 0.5% moxifloxacin eye ointment containing soft paraffin as the base.

Keywords: 20% fluorescein dye, lice, phthiriasis palpebrarum, phthiriasis pubis

PHOTO ESSAY

A 39-year-old female presented to our OPD with complaints of severe itching of left eye of one-month duration which was previously misdiagnosed as anterior blepharitis. Several lice and multiple nits were noted on the eyelashes in her left eye under slit-lamp examination [Figure 1a and b]. Her best-corrected visual acuity was normal in both eyes. The patient was managed by mechanical removal of lice and nits after applying 20% fluorescein dye and subsequent treatment with 0.5% moxifloxacin eye ointment containing soft paraffin as the base. After instillation of topical anesthesia (proparacaine eye drops) on the conjunctival cul-de-sac, the patient was asked to gently close the lids. Twenty percent fluorescein dye was then applied over the eye lashes and eye brows of both the eyes with the help of sterile cotton-tipped applicator. Thirty minutes were allowed for the fluorescein dye to dry and to have its effect on the parasites. The patient was instructed to keep her lids closed during this period. The remaining adult parasites and nits were mechanically removed with the help of blunt forceps. She was then prescribed 0.5% moxifloxacin eye ointment with soft paraffin as the base, for thrice daily application, for 10 days. She was seen 1 week later and few nits were remaining. The same procedure of mechanical removal after application of 20% fluorescein dye was repeated in order to remove the remaining nits. She was again seen after 1 week and after 1 month. Her lids were clean and completely parasite free at these follow-up visits [Figure 2]. The patient was advised dermatology consultation.

DISCUSSION

Phthiriasis palpebrarum is an ectoparasites of the eyelashes because of an infestation with phthiriasis pubis, also known as pubic louse or crab louse. It is a rare entity and can be confused with blepharitis.[1] Probably a large number of cases are being missed since it mimics anterior blepharitis clinically and often misdiagnosed as conjunctivitis or blepharitis.[2] The nits and adult lice harboring the lashes of the eye can also be easily missed. It can present with clinical features like excessive itching, lid hyperemia, and excoriated skin. It is frequently misdiagnosed as allergic conjunctivitis or blepharitis due to deep burial of the ectoparasites and the presence of crusts on the eyelashes.

Phthiriasis palpebrarum is caused by phthiriasis pubis, a hematophagous arthropod, an obligate parasite of human

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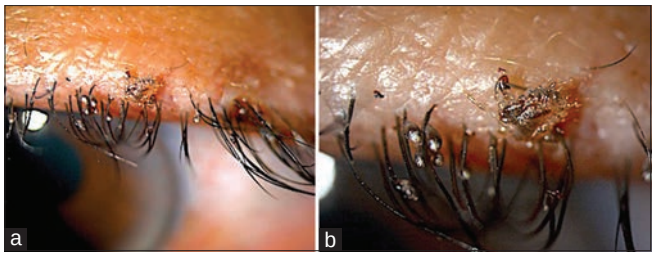


Figure 1: (a) Slit-lamp image showing louse with nits on the lid margin. (b) Magnified view of the parasite with nits

beings. It is an insect belonging to pthiridae family and phthiriasis genus. Adults measure up to 2 mm long and are smaller than the head lice and body lice.[1]

Infestation with phthiriasis pubis occurs mainly through sexual intercourse or during interactions between infested parents and their children. It generally affects both eyes and unilateral involvement is less common. But in our patient, we noted the infestation only in left eye.

Several topical treatments may be used in phthiriasis palpebrarum. This includes manual removal of adult parasites and nits using forceps, 0.3% tobramycin eye ointment, 0.5% moxifloxacin eye ointment with paraffin as the base, parasympathomimetic agents (physostigmine ointment, 4% pilocarpine gel), liquid Vaseline, topical botulinum toxin, 20% fluorescein dye, etc., Argon laser therapy, cryotherapy, 1% gamma-benzene hexachloride cream, 1% mercuric oxide ointment, malathion shampoo, permethrin 5% ointment, 50% tea-tree oil, and lindane are also described. Application of 20% fluorescein dye causes immobilization of parasites, facilitates their mechanical removal, and reduces the risk of accidental infestation of treating physician.[3] The paraffin base in ophthalmic ointment acts as a suffocating agent to kill the lice and the antibiotic component helps to prevent secondary bacterial infection. All sexual contacts and family members of the infested person should be evaluated for the presence of phthiriasis pubis and phthiriasis palpebrarum and if necessary, they have to be treated. The patients should get counseling regarding personal hygiene and cleaning of linens and clothing. The prognosis of phthiriasis palpebrarum is good in majority of cases.

Application of 20% fluorescein dye, mechanical removal of the parasites and nits, and topical application of ophthalmic ointment with paraffin base are effective in the treatment of phthiriasis palpebrarum.

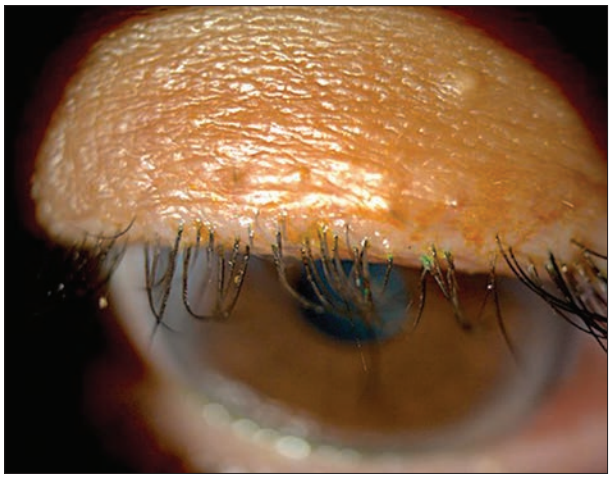


Figure 2: Slit-lamp image taken 2 weeks after starting treatment

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Declaration of patient consent

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Types of Study Designs

The study design is a framework of methods and procedures used to collect and analyze data in a particular research problem. Research study designs are of many types, each with its advantages and limitations. The type of study design used to answer a particular research question is determined by the nature of the question, the goal of the research, and the availability of resources. The research question should include 1) the defined population from which the study group is taken 2) the outcome that is measured 3) the time frame 4) Comparison group (in an analytical study) and 5) Intervention group (in an interventional study). Since the design of a study can affect the validity of its results, it is important to understand the different types of study designs and their strengths and limitations.

Study designs are broadly classified as observational and interventional studies.

• **Observational studies.**

Observational studies are those where the researcher is documenting a naturally occurring relationship between the exposure and the outcome. The researcher does not do any active intervention in any individual, and the exposure has already been decided naturally. For example, looking at the incidence of central retinal vein occlusion in those with and without hypertension.

In this study design, the researcher is just observing and analyzing the characteristics of particular groups of individuals. There is no active intervention in the form of either medicines or any surgical intervention.

This itself may be classified as a descriptive or analytical study.

DESCRIPTIVE STUDY

Descriptive (or non-analytical) studies merely describe the data on one or more characteristics of a group of individuals.[1] These do not try to answer questions or establish relationships between variables. These types of studies can generate hypotheses. Examples of descriptive studies include case reports, case series, and cross-sectional surveys (please note that cross-sectional surveys may be analytical studies as well).

For example, we are observing a group of individuals with a corneal ulcer in our institution. We observe the characteristics of this group of patients. We can find out the number of patients with a fungal, bacterial, or viral corneal ulcer. The baseline characteristics of these individuals can be studied. There is no control group in this type of study.

Case report

Osler one of the fathers of modern medicine stated that "Always note and record the unusual….Publish it"

A case report is a "detailed description of a few patients or clinical cases with an unusual disease or complication, uncommon combinations of diseases and unusual or misleading semiology, cause or outcome."[2]

The value of case reports is usually underestimated when compared to other studies which are supported by evidence. Case reports have indeed led to discoveries and the introduction of treatments for novel diseases.

Case series

According to the latest version of the Dictionary of Epidemiology a case series is defined as a " collection of patients with common characteristics used to describe some clinical, pathophysiological or operational aspects of a disease, treatment or diagnostic procedures"[2]

In the review article "Clinical case series: a conceptual analysis" published in the Journal of African health sciences, FM Abu-Zidan *et al*.[3] reviewed 586 papers and suggested that a case series should have more than 4 patients while 4 or fewer patients should be reported as case reports.

One of the reasons behind this is that, if data of a group of subjects are to be summarized statistically, a minimum number of subjects is needed to be valid. Five is the minimum number needed because the standard error of the mean, which is used for comparison will be much larger if the number is less than five.

Cross-sectional surveys

This type of study is a transverse type of study design which includes a larger number of patients who are evaluated at a single time without any follow-up. There is no comparison

group. Both the cause and effect have already occurred. It can measure the prevalence of a disease or risk factor. It cannot find out the cause-and-effect relation. It is easy to conduct.

For example, a cross-sectional survey may be conducted to find out the prevalence of presumed ocular tuberculosis by studying a group of patients with the disease.

ANALYTICAL STUDY

This type of study design attempts to test a hypothesis and aims to find out a cause-and-effect relationship.[4] The researcher tries to find out the effect of exposure on the outcome or risk factor of a particular disease. They can be of different types.

Cross-sectional analytical study

As described earlier this is a transverse type of study design and the difference with the descriptive cross-sectional survey is that there will be a comparison group in an analytical cross-sectional study.

Cohort study

"Cohort" term refers to a group of individuals with a shared characteristic 9. In a cohort study, individuals with or without a risk factor are followed up over time to know about the occurrence of a disease or an outcome. So, it is a forward direction study (moving from exposure to the outcome) or "prospective study." It helps to find out the risk of disease or outcome among those with the risk factor compared to those without the risk factor. (Relative risk-RR)

Example: Individuals with and without thyroid disorders are followed up for the occurrence of primary open-angle glaucoma.

Advantages:

1. Risk of outcome among exposed and unexposed can be studied.
2. It can be ensured that exposure occurred before the outcome.
3. Multiple outcomes to exposure can be analyzed.
4. It closely resembles interventional study except for the lack of random assignment of exposure and hence it has the strongest validity among observational studies.

Limitations

1. Long follow-up is needed in most cases.
2. Confounding factors may affect the outcome. In the above example where those with and without thyroid disorders were followed up for the development of glaucoma, the confounding factors may be diabetes, coronary artery disease, etc., which may also predispose to the development of glaucoma.

Variation of a cohort study:

Retrospective cohort study: Although cohort studies are prospective, in some situations retrospective cohort study can also be done. For example, in the above-mentioned study if the researcher includes patients with and without thyroid disorder from the hospital records 5 years back and then calls up these patients to see whether they have developed glaucoma, then this becomes a retrospective cohort. Here the direction is always forward i.e., from exposure to the outcome, but since the outcome has already occurred this becomes a retrospective study.

Case control study

The researcher selects cases (with disease or outcome) and controls (without disease or outcome) and then tries to find out the history of exposure among these two groups. These are backward-directed studies and are always retrospective as the outcome has already occurred.

Identification of controls is of key importance in the case-control study as this may influence the estimation of the association between exposure and outcome. The control should be similar to cases in all aspects except for the absence of disease.

Example: All preterm babies with (cases) and without ROP (controls) were included and the duration of exposure to oxygen during the neonatal period was analyzed in the two groups.

Advantages

1. Easy to perform
2. Less time consuming
3. Multiple risk factors can be studied.
4. It can be used for studying rare diseases.
5. Since it is easy to perform these are usually done as an initial study over which further complex studies like cohort or interventional studies can be done.

Limitations

1. Improper selection of controls can lead to selection bias.
2. Since it is a retrospective study the data collection depends on the credibility of the records.
3. Confounding factors may play a role here also.
4. It cannot be ensured that exposure occurred before the outcome of interest.
5. We cannot estimate the risk ratio, can measure only the odds ratio.

Variation of case-control study:

NESTED CASE-CONTROL STUDY:

It is a part of the cohort study. Two groups of individuals with and without risk factors are included and followed up for the development of an outcome or a disease. During the due course, some may develop the outcome of interest and they will be selected as cases and the other group who have not developed the disease will be selected as controls. Here the advantage is that irrespective of being a retrospective study it can be ensured that exposure occurred before the disease or outcome of interest.

Interventional study

In the interventional study design, the researcher is actively involved in the process by performing an intervention in some or all participants.[5] This design is prospective by its nature. Sometimes confusion may arise between a prospective cohort study and an interventional study. The only difference is that in interventional studies the researcher assigns each person for the intervention whereas in a cohort study the intervention or exposure is already decided.[1]

Broadly speaking interventional studies can be divided into two:

1. Clinical trials
2. Community trials.

It can also be divided into preventive trials or therapeutic trials depending upon whether the intervention includes preventive measurements or therapeutic measures.

Several variations of interventional study designs are there which include:

1. Randomized controlled trials
2. Non-Randomized controlled trials
3. Interventional studies without concurrent controls
4. Before-After or Pre-Post studies
5. Factorial study design
6. Crossover study design
7. Cluster Randomized trials.

Randomized controlled trials

Participants fulfilling the inclusion and exclusion criteria are randomly assigned into two groups with different interventions or one group with any other group without intervention. Randomization means that each participant has an equal chance of being allocated into each group. The two groups are similar in all aspects except for the intervention so the two groups are comparable. Some additional features are usually added to this type of study design like allocation concealment, blinding, intend-to-treat analysis, measurement of compliance, minimizing dropouts, and ensuring appropriate sample size.

Nonrandomized controlled trials

The allocation to two groups is not Randomized. For example, the investigator may decide which participant is to be allotted to one group based on availability or affordability. So, the two groups may not be comparable and so the validity of this study is also low.

Interventional studies without concurrent controls

When a new intervention or a drug is invented the researcher can compare those who have received the drug or intervention to a group of individuals who were followed up in the past and have not received the treatment. This includes a lot of bias.

Before-after or pre-post studies

A variable is measured in the same group of participants before and after an intervention. There is no comparable group. The particular outcome may be related to other changes that might have occurred at the same time as the intervention. Thus, the outcome in such studies may not be attributed to the intervention making it a weaker study design than RCT. Some include this study design as an observational study design rather than an interventional study design.

Factorial study design

When there are two or more interventions for a particular disease, we can find out whether each intervention is efficacious or whether a combination of these two interventions is efficacious or not.

For example, if there are two interventions A and B, we can allot participants to any of the four combinations of interventions.

1. A alone
2. B alone
3. A and B
4. None of A or B.

So, we can find out the effect of interventions A and B, the combination of A and B, and compare with the controls (not receiving A or B). So, in this single study, we can compare the effect of two interventions and the effect of their combination too.

Cross-over study design

This is a type of study design in which the study participants intentionally switch over to the other arm of intervention. At

the start of the study, participants are allotted to a particular intervention group based on random allocation and after some period they will be switched over to the other arm. The other type of study design where the participants don't have a crossover is called parallel-arm RCT.

The advantages of this type of study design

1. Each person serves as a control for himself.
2. Requires a smaller number of participants when compared to parallel arm study.
3. It is possible only in some types of diseases and interventions.

Cluster randomized trials

In some situations, a particular intervention cannot be applied to individuals but can be administered to groups. A cluster of individuals can be allotted to an intervention group and other clusters to the other arm.

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PROGRESSION PATTERNS OF NORMAL-TENSION GLAUCOMA GROUPS CLASSIFIED BY HIERARCHICAL CLUSTER ANALYSIS

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The authors did a retrospective cohort study to compare the differences in progression patterns in normal-tension glaucoma (NTG) patients classified into three clusters using hierarchical cluster analysis (HCA). The authors concluded that the pattern of progression differed by NTG groups, and that young myopic eyes showed a mixture of two patterns. HCA is an analytical method in which similar characteristics are identified and divided into clusters by an automated computer program. NTG is a multifactorial optic neuropathy with different progression rates for each patient. According to the Collaborative Normal-Tension Glaucoma Study (CNTGS), NTG in half of the untreated patients did not progress for 5–7 years. In this study, peripapillary retinal nerve fiber layer (RNFL) thickness was measured by Cirrus HD_optical coherence tomography (OCT) and progression rate was calculated by trend analysis (Guided Progression Analysis [GPA]). The visual field (VF) progression rate was evaluated by linear regression analysis of mean deviation (MD). Cluster 1 had small cupping with thick RNFL suggestive of early glaucoma patients. Cluster 2 exhibited moderate glaucoma findings. Cluster 3 had young, myopic patients. One-way analysis of variance (ANOVA) was used to analyze differences between clusters, and Bonferroni post-hoc test was performed to assess statistical significance between clusters. The progressive rate distribution of each cluster was represented by a histogram.

Cluster 1 exhibited the fastest progression rate on OCT, with a decrease in average RNFL thickness of -0.83 ± 0.89 μm/year. The progression rates for cluster 2 and 3 were -0.45 ± 0.76 μm/year and -0.36 ± 0.79 μm/year, respectively ($P < 0.011$). There were no significant differences in the baseline intraocular pressure (IOP) among groups. The mean IOP and fluctuations during the follow-up period were not significantly different among clusters. The mean number of IOP lowering agents was significantly less in cluster 1.

Regarding the average RNFL thickness progression rate for each cluster, cluster 1 progressed the fastest and was skewed toward the negative progression rate section. Cluster 2 exhibited a normal distribution with many patients falling in the range of 0 to -1.0 μm. Cluster 3 displayed a double-peak distribution. Patients in cluster 3 were divided into two groups and their characteristics were compared.

Cluster 1 had the fastest visual field progression rate (-0.16 ± 0.61 dB/year), but clinically, there was no significant progression difference among the three clusters in VF tests. This is probably because most patients enrolled in this study were at an early to moderate stage, and because the structural abnormalities are typically detected in OCT before VF defects occur. Also, these patients were managed effectively with IOP lowering drugs.

IOP was decreased approximately 20% from baseline. Less number of medications were used in cluster 1, in contrast, patients were administered more topical drugs in cluster 2. This may explain why cluster 2 progressed less than cluster 1. There was no significant difference in progression rates between clusters 2 and 3 and it was further analyzed by a histogram. The distribution of progression in cluster 3 showed a double-peak pattern, unlike other clusters, suggesting that one group showed rapid progression like cluster 1, and the other group hardly progressed. Glaucomatous damage progressed in both the superior and inferior RNFL of those in the fast progression group.

There are widespread disputes regarding glaucoma progression in myopic patients. One opinion is that it progresses regardless of the degree of myopia or that it progresses less than other types of glaucoma without myopia. However, in this study, the progression of myopic glaucoma did not exhibit a single phenomenon, suggesting the presence of at least two patterns with different characteristics: "progress" and "non-progress." In the progress group, myopia may have increased glaucoma susceptibility. Kim *et al.*[1] reported that eyes with a particular posterior sclera structure are at increased risk for glaucoma progression in treated myopic NTG patients. Sohn *et al.*[2] found out that myopia did not influence the progression rate of NTG after treatment. Limitations of this study include follow-up loss and reduction in sample size. The use of medications was not adjusted in this study.

Bae *et al.*[3] predicted that inferotemporal RNFL thinning could be a risk factor for progression in NTG patients with myopia. In a study conducted by Han *et al.*,[4] younger age, presence of disc hemorrhage, more temporally tilted disc, and parapapillary atrophy were associated with progression.

It also showed that NTG with myopia progressed very slowly even without antiglaucoma drugs. Only 10.3% and 24.8% of patients showed VF progression at 3 years and 5 years of follow-up in untreated NTG with myopia. Higher long-term fluctuation of IOP was associated with faster VF progression rates only in myopic NTG according to Lee *et al*.[5] Jonas *et al.*[6] also observed that structural changes of the sclera in myopia increase stress and strain on the lamina cribrosa, thereby increasing glaucoma susceptibility. Patients with NTG and superior field defects had significantly faster progression rates than patients with inferior field defects, and the difference in the progression rates was more observed in the central and nasal zones.[7]

The complex etiology of NTG is not yet completely understood. In fact, early NTG is missed and not assessed appropriately since there is no severe damage, but early glaucoma with a low cup-to-disc ratio can progress faster. Therefore, those patients should be vigorously treated with proper follow-ups. In the young myopic eyes, two types of progression patterns were noted and, in such patients, only the progressive cases should be actively identified and treated. Although practically, control of IOP remains the mainstay of treating NTG patients, we should also evaluate other risk factors, especially those that may influence perfusion of the optic nerve head.

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Myopia: Strategies to prevent progression

ABSTRACT

Myopia is becoming increasingly prevalent, posing a significant economic and social burden across the world. Myopia is one of the most common ocular disorders of the eye causing defective vision in young and adults, which is correctable by optical aids and surgical means. In addition to the disadvantages in terms of vision impairment, myopia increases the risk of myopic macular degeneration, retinal detachment, and cataract producing a significant effect on the quality of life as well. Progressive myopia can lead to potentially blinding complications. This article is aimed at discussing various interventions that can reduce the progression of myopia in childhood and include environmental considerations, pharmacological agents, and newer advances in spectacles and contact lenses.

Keywords: Atropine, myopia, orthokeratology, progressive addition lenses

INTRODUCTION

Myopia is defined as the dioptric condition of the eye in which incident parallel rays of light from infinity come to a focus anterior to the retina, with the accommodation of the eye at rest. The increasing prevalence of myopia, especially in this Corona virus disease-2019 (COVID-19) pandemic era is a major challenge worldwide, leading to an epidemic in certain regions.

Myopia develops and progresses in a predictable pattern, beginning with normal vision at a young age. A myopic shift and rapid growth in myopia begins around school age and lasts until late adolescence.[1] According to a meta-analysis in 2020, the prevalence of myopia among Indian school children was 8.5% in urban and 6.1% in rural populations, with the highest prevalence in urban 11- to 15-year age group children in the last decade.[2] High myopia is defined as a condition in which the spherical equivalent refractive error of an eye is − 6.00D or above when ocular accommodation is relaxed.[3] Progressive myopia can lead to potentially blinding complications. Through this article, we are shedding light on a few strategies to prevent myopia progression.

Risk factors for progression

In defining a child's refractive error status, genetics appear to play an important role. Parental myopia is a risk factor not just for having myopia, but also for developing progressive myopia in children.[4] Children with at least one myopic parent had higher rates of myopic progression than children without a myopic parent (0.63 diopters/year vs. 0.42 diopters/year, respectively), according to Saw *et al*.[5]

Lack of outdoor activities has been demonstrated to increase the incidence and progression of myopia.[6] Higher light intensity present outdoors is thought to increase the depth of focus and lessen image blur. Furthermore, light stimulates the release of dopamine from the retina, and dopamine can impede eye growth.[7] So high levels of ambient light can significantly delay the onset and progression of form-deprivation myopia.[8]

A few studies have identified a robust link between near work and myopia progression. Most people accommodate only a fraction of what is required to bring the target into

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focus. The gap between the accommodating stimulus and the observed accommodative response is used to quantify this underaccommodation, which is referred to as a lag of accommodation. The development and progression of myopia have been linked to a greater lag of accommodation in connection with near work.[9] Myopes may experience extended periods of retinal defocus as a result of poorer accommodation to near targets, which has been shown to contribute toward increased eye growth, particularly vitreous chamber elongation in animal models of myopia.[10] Children who live in an urban environment and spend little time outdoors and those who are doing excess of near work are at a greater risk of progressive myopia.

CONTROL OF MYOPIA PROGRESSION

Myopia progression can lead to significant sight-threatening complications, such as amblyopia, myopic macular degeneration (MMD), retinal detachment, and cataract.[11,12]

Chief beneficiaries of myopia control are children with low myopia who would otherwise progress to high myopia, with the attendant risks of visual morbidity later in life. The beginning of myopia at a younger age appears to be linked to a faster rate of progression.[13] The strategies for control of myopia progression include lifestyle modifications, pharmacological agents, and optical interventions. Despite lower efficacy, optical interventions may appear more appealing than pharmaceutical interventions because of the less significant side effects and the fact that myopic children are likely to wear an optical appliance anyway. Contact lens-based interventions generally appear to have a more robust effect in slowing myopia progression than spectacle-based interventions.[13] Knowledge of prior progression rate helps in deciding the appropriate intervention and it also provides a benchmark against which the efficacy of future treatment can be assessed. Initial cycloplegic refraction provides a baseline objective assessment before starting any intervention.

Lifestyle modification

The mechanism by which increased time spent outdoors is linked to a lower myopia incidence has not completely been elucidated so far. Animal models suggest that light exposure can stimulate retinal dopaminergic pathways, which then interfere with eye growth signaling pathways, preventing excessive elongation of the eyeball.[14] Variations in the chromatic light composition, differences in dioptric topographies, less near work, and a decrease in the accommodative demand are the other proposed reasons for the prevention of myopia incidence and progression.[15] Spending more than 2 h a day outside was linked to a lower risk of myopia, even in children who did a lot of near work.[7] A systematic review and meta-analysis were conducted to evaluate the effects of outdoor light exposure on myopia by Ciao-Lin Ho *et al.*,[16] and they suggest 10 h/week of outdoor light exposure time at school for myopia prevention. According to them, 10 h/week or 120 min/day can reduce myopia incidence by 63.7%. The risk of rapid myopia progression was 54% lower in children who spent at least 11 h/week outdoors at the end of 1 year according to the study done by Pei-Chang Wu *et al.* They also concluded that longer periods of relatively low outdoor light intensity, as in the shade of trees, maybe sufficient for the prevention of myopia onset and progression.[17]

Pharmacological agents to control myopia progression

Atropine eye drops

Atropine is a non-specific muscarinic acetylcholine receptor antagonist. The mechanism through which atropine slows down myopia progression is unknown. Two theories have been proposed to explain the action of atropine using experimental animal models. The first theory is that atropine binds to M1/M4 receptors in the retina and slows eyeball elongation through a neurochemical cascade; the second theory is that atropine directly inhibits glycosaminoglycan synthesis by scleral fibroblasts.[18] The Atropine for the Treatment of Myopia study (ATOM1) was a double-masked, randomized placebo-controlled trial of atropine eye drops, which involved 400 children with myopia in Singapore.[19] They found that the group which used 1% atropine eye drops in one eye every night for 2 years showed dramatic reduction in myopia progression and axial elongation when compared to the control group. The ATOM2 experiment looked at lower concentrations of atropine, such as 0.5%, 0.1%, and 0.01%, because 1% atropine caused allergic reactions, glare owing to pupil dilatation, photophobia, and blurry near vision due to cycloplegia.[20] When compared to 0.1% and 0.5% atropine, 0.01% atropine had fewer side effects and had a comparable effect on myopia progression. The 0.05% atropine was shown to be most effective in preventing myopia progression and axial elongation.[21]

The myopic rebound effect was more significant in eyes that got 1.0%, 0.5%, and 0.1% atropine than in eyes that received 0.01% atropine when treatment was stopped.[20] Previous studies showed that younger age and greater severity of myopia were risk factors for progression in a subgroup of children despite getting atropine treatment.[22]

In summary, there is a strong evidence that atropine can help delay the progression of myopia. Some long-term safety issues have not yet been addressed. However, the general consensus of the clinical studies is that the treatment is

safe. Lower concentrations (0.01% and 0.1%) of atropine are better tolerated and could be an excellent clinical choice.[23] However, the efficacy of the weaker doses of atropine could be a concern[24] A once- or twice-weekly application of high-concentration atropine (0.5% or 1.0%) could be an alternative therapy option.[23]

Pirenzepine is a selective muscarinic M1 acetylcholine receptor antagonist. According to a multicenter trial conducted in Hong Kong, it can also be utilized in the form of a 2% gel to prevent myopia progression.[25] However, the use of pirenzepine eye drops as a myopia reduction therapy was discontinued, and it is no longer available as a therapeutic option.[26]

Optical control of myopia progression

Myopia of −3 to −5 D does not provide a substantial risk of amblyopia since near vision is often unaffected. Low myopes should have their glasses prescribed when they are three to four years old, as this is when they begin to spend considerable time looking at things far away. If the power is greater than −3D, glasses should be prescribed even in less than 3-year-old children. The goal is to prescribe the least amount of minus power necessary for the optimal visual acuity, and over-correction should be avoided at all costs.[27] According to recent research, under-correction may accelerate instead of slowing down myopic progression in children.[28] Six monthly reviews have to be done to watch for progression of myopia, if a single vision spectacle for correction is given.[26] It is critical to stick to the recommended wearing time and have regular clinical reviews.

Bifocal or progressive addition spectacles (PALs)

The fundamental mechanism by which progressive addition lenses reduce myopic progression is by minimizing accommodative lag during near work. This reduces retinal hyperopic blur which is a stimulus for the growth of eyeball.[29] It has been proposed that PALs are a better alternative to bifocal lenses because they provide clear vision at all distances and are more cosmetically pleasing, potentially improving compliance. A near addition of +1D to +2 D was found to be effective in reducing the progression of myopia. One reason why bifocal or PAL spectacles have not been very effective in delaying myopia progression is that children prefer to observe near objects through the distance portion of the spectacle lens rather than the near addition.

Correction of Myopia Evaluation Trial (COMET) is a randomized, double-masked, controlled clinical trial that compares the progression of myopia in children wearing PALs to children wearing standard single vision lenses (SVLs). Over a 3-year follow-up period, progression of myopia was significantly less in PAL group (+2D add) than in SVL group. Children wearing PALs had a mean increase in the spherical equivalent of −1.28D and axial length of only 0.64 mm compared to −1.48D and 0.75 mm in the case of the SVL group.[30]

Multifocal soft contact lenses

Multifocal soft contact lenses usually feature circular zones of varying power within them to let the eye concentrate on both far-away and close-up objects at the same time. Recently, a novel dual-focus (DF) soft contact lens, with a central correction zone and concentric treatment zones that simultaneously create myopic retinal defocus (focal point anterior to the retina), has successfully been shown to reduce the progression of both the myopic refractive error and the abnormal axial elongation of the eye.[31] The safest approach to wearing contact lenses is using daily disposable lenses. A child has to wear soft multifocal contact lenses for most of the waking hours for 6 to 7 days a week. According to Walline *et al.*,[32] soft multifocal contact lens wear resulted in a 50% reduction in the progression of myopia and a 29% reduction in axial elongation during the 2-year treatment period compared to the control group.

Orthokeratology (Ortho K)

Ortho K lenses consist of reverse geometry contact lenses that are worn overnight by children and removed when they wake up. It involves precise fitting of rigid contact lenses during nighttime. To restore clear vision, the central area of the cornea is flattened and this approach allows for spectacle-free vision throughout the day, while the mid-peripheral area is steepened to control myopia progression.[33] The current explanation for how Ortho K lenses might delay myopia progression is based on a shift in the position and shape of the image shell relative to the peripheral retina. Several investigations have documented this shift in peripheral refraction from predominantly hyperopic to predominantly myopic peripheral retinal defocus.[13] Contact lens application in youngsters can be challenging; this is greater in younger children. In addition, during the nocturnal usage of any contact lens, there is an inherently increased risk of corneal infection. The use of orthokeratology in high myopes is complicated by the natural rebound to its original corneal contour over the day, as there is a myopic shift toward the end of the day, which leads to decreasing vision over time.[34] Orthokeratology lenses are only worn at night and hence at home, parents will be able to monitor every element of use. The inhibitory effect of Ortho K lenses on axial elongation for 2 years has been reported to be from 32% to 63%, as compared with single-vision spectacles and contact lenses.[35]

Newer myopia control options

The status of the peripheral retina's refractive state can have an impact on eye growth.[36] Peripheral hyperopic retinal defocus was first suggested as a risk factor for myopia in the 1970's.[37] Based on the experiments in animals, it has been hypothesized that peripheral retinal hyperopic defocus in the human eye can cause accelerated eye growth. Therefore, optical lenses that either eliminate peripheral hyperopic defocus or produce myopic peripheral defocus slow the progression of myopia in children[38] [Figure 1].

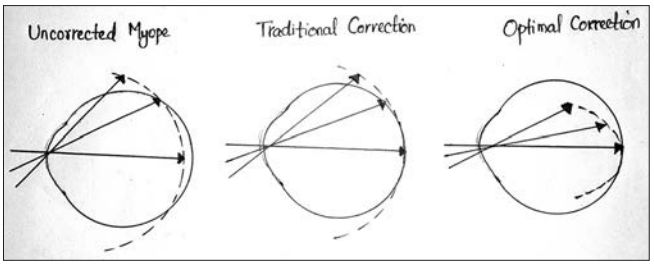


Figure 1: Peripheral retinal hyperopic defocus causing progression of myopia

Defocus incorporated soft contact (DISC) lens achieve peripheral retinal myopic defocus by incorporating concentric rings that provide addition of +2.5 D, in a manner that alternates with normal distance correction. Over a 1-year period, significant reductions in myopia progression and axial elongation were noted in the DISC group according to a randomized control trial performed in Hong Kong.[39]

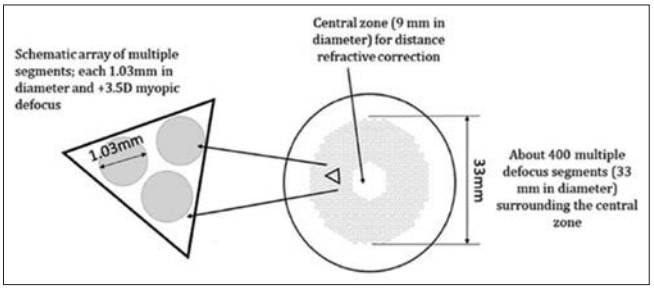


Figure 2: Defocus incorporated multiple segments lens designs (open access journal-Lam CSY, *et al*. Br J Ophthalmol: 104:363-368. doi: 10'1136/bjophthalmol-2018-313739)

Defocus incorporated multiple segments (DIMS) spectacle lenses were designed later to avoid the inconvenience and risk of contact lens use in youngsters. The lenses have a central optical zone that corrects myopia, as well as several segments of myopic defocus that stretch from the central zone to the lens's mid-periphery. The DIMS technology is based on the idea of creating simultaneous defocus during both distance and near viewing; one plane on the retina due to the lens' single vision zone (s) and one plane creating myopic defocus due to the + 3.50D defocus lenslets. DIMS had no effect on near phoria or accommodation lag[40] [Figure 2].

Highly Aspherical Lenslet Target (H.A.L.T.) technology also aims at peripheral retinal defocus, thereby reducing myopic progression. Rather than concentrating light on two different surfaces, these aspherical lenses deviate rays of light in a nonlinear fashion, creating a three-dimensional quantity of light in front of the retina, called as the volume of myopic defocus.[41] These lenses consist of aspherical front surface with 11 concentric rings formed by lenslets of diameter 1.1 mm. The area without lenslets provides distance correction [Figure 3].

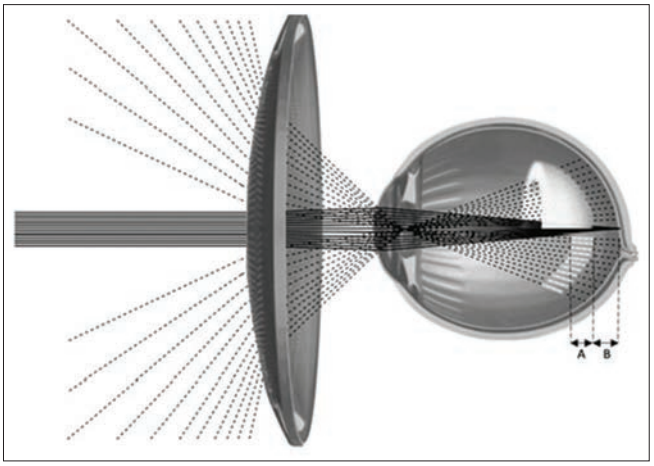


Figure 3: HALT lens technology (open access journal- Jinhua Bao *et al*. Br J Ophthalmol doi: 10.1136/bjophthalmol-2020-318367)

COMBINED THERAPY

Practitioners may think about combining the effects of more than one technique in cases of excessive myopia or exceptionally high rate of progression. Partially correcting vision using Ortho K lenses overnight and low-powered eyewear during the day is a viable solution. When considering other methods, care must be taken to ensure that the two strategies complement each other or at the very least do not work in opposition to one another. For example, the favorable effect of contact lenses for peripheral retinal defocus, which rely on active accommodation to deliver myopic retinal defocus during near tasks, may not be boosted by concurrent use of atropine 1%, which paralyzes accommodation.

UNDER TRIAL

Myopia X, a digital treatment to delay the progression of myopia, is a multicenter randomized control trial to see if it is safe and effective.[42] Artificial intelligence (AI) and other digital technological solutions have emerged as a viable adjunct for myopia management. Machine learning (ML), deep learning (DL), genomics, and natural language processing (NLP) are the four major AI disciplines in myopia.

The majority of current AI research in myopia is focused on illness classification and prediction. By aggregating a wider range of criteria, such as genetics and environmental factors, AI will play an increasingly important role in large data analysis which may enable the development of a deep learning system. This could help us in developing a precise treatment that is both predictive and customized.[43] A study is now recruiting participants to test the efficacy of DIMS lenses and Apollo progressive addition spectacles (PALs) in preventing myopia progression in children aged 6 to 12 years.[44] The Personalized Addition Lenses Clinical Trial is a recent trial which compares the progressive addition lenses (PALs) with customized additional power, against standard +2.00D PALs and Single vision lenses.[45]

CONCLUSION

Prevention of myopia progression is very important to prevent its potentially blinding complications. Pharmacological and optical interventions along with lifestyle modification have made many contributions toward preventing the progression of myopia to some extent according to various studies. Interventions at the genetic level to tackle the problem of myopia and its progression have not been studied much. Future studies should aim at preventing the onset of myopia itself as the burden of the disease is increasing worldwide.

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Comments on: Off-center presentation of ocular myasthenia

The case report "Off-center Presentation of Ocular Myasthenia" by Dr. Mary A. Stephen has highlighted the case report of a 70-year-old diabetic male who presented with diplopia.[1] The article brilliantly described a presentation of ocular myasthenia and highlighted the need for a high degree of suspicion for timely diagnosis of ocular Myasthenia Gravis. In this case, the initial diagnosis of diabetic mononeuropathy changed to ocular myasthenia when the initial presentation of unilateral ptosis gradually evolved to bilateral ptosis. Early detection of myasthenia is important as the management of diabetic mononeuropathy is entirely different from that of myasthenia, which the author achieved by meticulous examination of the patient and by timely clinical suspicion.

From an academic point of view, the few points that I would like to contribute include:

1. Thoracic imaging like MRI or CT scan could have been done to detect thymoma, as it is present in 15% of cases.[2,3]
2. Testing for striational antibodies can help determine the severity as it is a marker of severe Myasthenia Gravis (MG). Nearly all patients with MG and thymoma and half of the late-onset MG subgroup demonstrate the presence of striational antibody.[4]
3. In seropositive cases, the titers of AchR (Acetylcholine Receptor) antibody are found to be significantly higher in patients who progressed to generalized disease than those whom it remained as ocular.[5]

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Conflicts of interest

There are no conflicts of interest.

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Waardenburg syndrome – diagnostic criteria – A puzzle

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The article by Shruthy Vaishali Ramesh *et al*. (KJO Vol. 34 Issue 2) has excellently illustrated the disease entity and diagnostic criteria of van der Hoeve-Halbertsma-Waardenburg syndrome. The neonate underwent an in-depth examination by the authors and with the major and minor criteria, they diagnosed the syndrome. The parents were also examined and genetic counseling was given which is an essential part of the rehabilitation of the child, was also meticulously done by the authors.

There are a few things that I would want to share from an academic perspective.

a. The white forelock (Leucismus pilorum (poliosis)) mentioned in the major criteria can disappear after the neonatal period,[1] hence this feature of the syndrome is not peculiar to it, but a white forelock may be inherited as a separate entity.[2]
b. It is mostly inherited in an autosomal dominant pattern. Type 1 is usually autosomal dominant, only type 4 has a recessive inheritance. In this scenario, authors were suggesting a possibility of autosomal recessive inheritance, though it was categorized as type 1.[3]

A family showing all the stigmata of Waardenburg syndrome in three generations and a plastic operation to correct the most commonly described feature has been comprehensively described by Cant and Martin in 1963.[3]

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