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Contents

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MINIREVIEWS

Binocular disturbance after glaucoma drainage device implantation

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Abstract

Binocular vision disturbance is a well-described complication of glaucoma drainage device (GDD) implantation. The pathophysiology is not well-understood, but may involve bulk effects from the implant and surrounding bleb, as well as modulation of muscle function due to surgical trauma and post-operative inflammation, resulting in a combined resection/posterior fixation effect. Retrospective studies have found the risks of motility disorder and diplopia vary widely, estimated to be 56%-86% and 57%-75%, respectively. More recently, cross-sectional studies and prospective trials estimate post-GDD incidence to be approximately 1%-44%, with the incidence in newer generation of implants designed to limit bleb size likely lower at 1%-5%. Suggested methods of management strategies include prismatic spectacles, monocular occlusion, extreme monovision, and strabismus surgery.

Key words: Glaucoma; Drainage; Implant; Device; Diplopia; Motility; Binocular; Disturbance; Strabismus

Core tip: The reported incidence of binocular disturbance after glaucoma drainage device (GDD) implantation is variable due to inconsistent study designs, disturbance definition and lack of pre-operative baseline evaluations. The incidence of motility disorder is likely higher than persistent diplopia, as some glaucoma patients requiring GDD are functionally monocular. The mechanism or disturbance is not well-understood, but the bulk of implant/bleb, changes in muscle length, tension and strength may result in a combined resection/posterior-fixation effect. Post-GDD diplopia may resolve spontaneously in some instances, while the intractable cases are usually managed with prismatic spectacles.

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INTRODUCTION

New onset, persistent binocular disturbance is a well-described complication of glaucoma drainage device (GDD) implantation[1]. Studies estimate the risk of post-GDD binocular disturbance to be between 2%-18%[2-10]. Broad categories such as "strabismus," "diplopia," "motility disorder," and "motility disturbance" are used to capture all cases of post-operative binocular disturbances without articulating their natures. The incidences of post-GDD binocular disturbance are often reported as complications in prospective trials or retrospective case series designed to assess the implants' efficacy in controlling intraocular pressure. Additionally, most of these studies lack rigorous pre-operative motility and binocular function evaluation, and the reports of post-operative binocular disturbances are often descriptive with no quantitative measurements. Assuming that the motility evaluations in these studies were triggered by the patients' complaint of diplopia, it

may be reasonable to assume that the true incidence of diplopia (especially if intermittent) and asymptomatic motility disturbances to be underestimated. Furthermore, intentional or unintentional post-operative anisometropia may result in decompensation of long-standing phoria and diplopia, which should not be attributed to the glaucoma drainage device implantation.

PATHOPHYSIOLOGY

The pathophysiology of binocular disturbance after GDD implantation is not well-understood, and the proposed mechanisms would include bulk effect, paresis, posterior fixation effect, and mechanical restriction. Earlier case reports suggest the implant or a large filtering bleb around the implant exerts a bulk effect on the globe, causing duction limitations in the direction of the implant[11-16]. Approximately 36% of patients in a retrospective series of double-plated Molteno implants had paretic strabismus in the muscle or muscles concordant to the quadrants of the implant. This suggests that muscle manipulation may result in injuries and paresis, and secondarily motility disturbance[17]. In other reports, a heterotropic, post-GDD eye deviates toward the implant 46%-100% of the time[1,17-21], implying a restrictive mechanism. During strabismus surgery to correct post-GDD strabismus, Roizen *et al*[22] noted uniformly restricted forced duction tests and presence of thick, fibrous capsule surrounding the implant and adjacent muscles, regardless of pattern of motility disorder. It is plausible that after the GDD implantation, the post-surgical inflammatory changes, development of the bleb and presence of muscle injury result in altered muscle length-tension relationship as well as a posterior fixation effect. Glaucomatous visual field loss may increase the risk of binocular disturbance due to brittle fusional ability from damaged peri-foveal visual fields and reduced binocular stimulation. This may suggest that patients with long-standing strabismus (presence of suppression) and/or greater visual field loss may be at higher risk of post-operative binocular disturbance. However, the tube versus trabeculectomy (TVT) study found that the mean deviation on automated visual field and prevalence of preoperative motility disturbance did not differ between those who had new-onset diplopia after GDD compared to those who did not, possibly due to insufficient power[20].

INCIDENCE OF POST-GDD BINOCULAR DISTURBANCES IN ADULTS

Binocular disturbance includes motility disorder, heterotropia and binocular diplopia, which describe a spectrum of dysfunctions ranging from limited ductional deficits to disrupted binocular cooperation. These entities can exist alone or, more frequently, in combination. General ophthalmic surgical approaches, especially when involving a peri- or retrobulbar infiltrate of local anesthetic agents, may result in binocular disturbances even when the extraocular muscles are not manipulated, although the risk is likely small. This provides a context of background incidence in which the incidence attributed to GDD can be elucidated. In a retrospective review of 20453 cataract cases performed under retrobulbar block with ropivacaine diluted with hyaluronidase, persistent diplopia was noted in 19 (0.093%) patients[23]. A similar survey of 2024 patients who had undergone cataract surgery with peri- or retrobulbar block yields an overall incidence of 0.25%[24]. Neither study includes a pre-operative assessment of motility and binocular function, but the reported incidences are adequate estimates of diplopia after procedures involving peri- or retrobulbar block anesthesia.

Retrospective studies on post-GDD binocular disturbance are often case series of consecutive glaucoma patients receiving implants or cross-sectional studies of diplopic patients referred to strabismus clinic who have previously received GDD implantation. In both scenarios, the patients originate from the glaucoma service and had undergone strabismus evaluation only after the onset of binocular disturbance, making baseline motility and binocular function tests rarely available. Frank *et al*[18] reviewed 7 patients who had undergone Krupin valve implantation, and found four patients (57%) with intermittent or constant diplopia, with the other three patients being functionally monocular. Six of the seven patients (86%) had significant deviation in primary position post-operatively[18]. Smith *et al*[21] described 37 eyes of 36 patients that had received Baerveldt glaucoma implant, with 5 of the 36 patient having documented motility disturbance and none with diplopia. Post-operatively, 23 of 30 eyes (77%) with adequate motility follow-up demonstrated motility restriction, and 11 of 17 (65%) binocular patients experienced diplopia[21]. It is not clear whether any or all of the 5 patients with pre-existing binocular disturbance were included in the follow-up. Wilson-Holt et al reported 16 eyes of 16 patients who had inferior surgical implantation of double-plate Molteno tubes and found 9 of the 16 patients (56%) developed a significant hypertropia, which averaged 8.9 prism diopters (range 2-15 prism diopters). The time of onset of diplopia and hypertropia after tube surgery ranged from 1 to 4 mo. All patients showed restriction on depression of the globe[25].

Taken together, one can infer from these three studies that the risk of motility disorder after GDD implantation in a glaucoma cohort ranges between 56%-86% and risk of diplopia between 57%-75%. Some patients develop heterotropia but not diplopia from being functionally monocular. It should be noted that some of these case series involve older generations of glaucoma drainage devices without modifications to modulate bleb size, thus the risks of motility disturbance and diplopia may be lower today with the newer generation devices.

Looking specifically at a group of patients carrying the diagnosis of "diplopia" or who had procedural codes for strabismus surgery, Abdelaziz *et al*[1] used financial claims information to identify patients who had undergone GDD surgery between 1991 and 2005 at a large ter-

tiary referral center[1]. After review of medical records to exclude diplopia or strabismus surgeries unrelated to the GDD, 1.4% of these patients had persistent, new-onset diplopia attributed to GDD implantation at one year. Despite the meticulous search methodology, the retrospective design and use of financial claims information is likely to underestimate the true incidence of new-onset, persistent diplopia after GDD implantation, especially if the diplopia diagnosis was not submitted for financial claims, or if the patients were lost to follow up.

Few prospective studies evaluated the effect of GDD implantation on motility. In a prospective, consecutive observational series, Dobler-Dixon *et al*[17] performed pre- and post-GDD (double-plated Molteno implant) sensory-motor testing on 24 patients undergoing GDD implantation. The majority had between 1 to 3 prior ocular surgeries. Eight patients (33%) had pre-existing motility disturbance, and 15 patients (63%) were binocular (defined as Snellen visual acuity of 20/70 or better in both eyes). New-onset, persistent motility disorder was noted in 11 of 24 patients (46%) after GDD implantation, 91% of which occurred in binocular patients. Seven of the 16 patients (44%) with normal pre-operative motility developed new-onset, persistent diplopia after GDD implantation, which were confirmed with red glass test. The authors further delineated the mechanism of strabismus to be paretic in 4 of the 11 patients, with high concordance of the paretic muscle being in the same quadrant as the implant, suggesting paresis associated with hardware implantation and intraoperative manipulation of the extraocular muscles during GDD implantation. However, the determination of paretic versus restrictive mechanisms and relative saccade velocities were not reported. The high likelihood of post-GDD motility disturbance in this series compared to the other studies may be attributed to meticulous post-GDD motility evaluations, which makes under-reporting less likely. The implant's double-plated design also requires access to multiple quadrants and larger peritomies, and the surgical technique requires elevation of at least one muscle in order to pass the distal plate underneath to the other quadrant.

The TVT Study included a formal motility evaluation on all patients at pre-operative baseline and at the 1-year follow-up visit[20]. A total of 101 patients were randomized to the tube group, 71% of whom were binocular (defined as Snellen visual acuity of better than 20/200 in both eyes). Pre-operatively, 26% of GDD patients were heterotropic (most commonly exodeviation at near), while only 2% had diplopia. Post-operatively, new-onset persistent diplopia developed in 5% of patients. However, saccade velocity and sensory confirmation of diplopia were not part of the pre- or post-operative evaluation, and the definition of binocularity was broad. The baseline pre-operative prevalence of heterotropia (26%) was much higher than that estimated by a random sampling of Medicare beneficiaries (< 1%) in a comparable age group[26]. This implies that glaucoma diagnosis and history of prior ocular surgeries (cataract extraction, glaucoma filtering procedures) may confer a higher risk of strabismus at baseline compared to the general population. Overall, the study's prospective design, large number of subjects and pre- and post-operative motility assessment makes it one of the more convincing reports on binocular disturbance after GDD implantation.

MANAGEMENT STRATEGIES

Anecdotally, many instances of motility disturbance will resolve without intervention within six months. However, if unresolved, the complex nature of post-operative binocular disturbance may require employment of a number of different strategies. Treatment is complicated by the variability of alignment during the healing process, incomitant nature of the deviations, torsion, and abnormal saccadic velocities.

Prismatic spectacle correction can be used as either a temporizing or a permanent solution, successfully alleviating symptoms in 65% of treated patients[1]. Prism correction can be used to facilitate fusion by aligning the images or by moving the second image further so that it can be suppressed. Its utility as a temporizing measure preceding strabismus surgery to test fusion or as a permanent measure to alleviate diplopia makes it extremely helpful in these complicated cases. The options include press-on Fresnel prisms for variable deviations or ground-in prisms for smaller, stable deviations.

Strabismus surgery may be indicated if the deviation is fairly comitant in a patient with adequate motor fusion; however, the patient must understand the goal of surgery is alleviation of diplopia in primary and reading positions and may not correct misalignment in other directions of gaze. The patient should be aware of the increased risk of compromised intraocular pressure control when operating next to filtering blebs and drainage devices. A multidisciplinary approach involving both strabismus and glaucoma services may increase the likelihood of success and minimize complications.

Alternatively, other surgical strategies include implanting a second implant in the opposite quadrant of the same eye (without or without removal of offending implant) or, when indicated, implanting a GDD in fellow eye under the yoke muscles. This strategy capitalizes on the observation that the implant may result in a combined resection/posterior-fixation effect, and thus decrease heterotropia. Aggressive lysis of adhesion with amniotic membrane grafts around the implant and affected muscles to reduce scarring have some anecdotal success.

Additionally, others have suggested extreme monovision in the form of glasses, contact lenses or intraocular lens implants as means to alleviate persistent diplopia by blurring the unwanted image and allowing suppression[27]. Lastly, while far from ideal, partial or complete occlusion of the involved eye with a patch, tape or foil may be the only option should resolution of the diplopia with alternate methods prove unsuccessful.

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MINIREVIEWS

Blue light induced retinal oxidative stress: Implications for macular degeneration

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Abstract

A number of studies have shown that oxidative stress can be harmful for the retina. The real causal circumstances that lead to degenerative diseases like age related macular degeneration remain obscure. Whether light induced radical stress is a direct interaction of light with photoreceptors or a secondary mechanism within the pigment epithelium or choroid is in discussion. Among the molecular mechanisms involved are production of reactive oxygen species (ROS), secondary lipid peroxidation, protein oxidation and DNA-damage. The initial trigger to write this review was first a recent finding of our group that the photoreceptor outer segments produce great amounts of ROS and second the detection of ectopic enzymes of the respiratory chain localized there - in addition to the hitherto known ROS sources like the visual pigments with their intermediates and the photoreceptor mitochondria harbouring the respiratory chain.

Key words: Blue light; Oxidative stress; Retina; Photoreceptor; Age related macular degeneration

Core tip: The role of blue light and oxidative stress in the pathogenesis of retinal degenerative diseases like age related macular degeneration is still under debate. Recent studies including ours have demonstrated that all molecules of the respiratory chain are present in the outer segment of the photoreceptors-also being the source of reactive oxygen species-even more than the reactive oxygen species production in inner segment mitochondria. These two new findings have also important implications for many degenerative diseases of the retina. In this respect we revisited the literature regarding the photoreceptor reactions after blue light and radical stress.

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INTRODUCTION

Age related macular degeneration (AMD) has-like many neurodegenerative diseases-a multifaceted genesis with genetic, metabolic, immune and environmental factors[1,2]. Blue light damage and oxidative stress are prominent among the environmental factors, which are discussed recently[3,4]. Comprehensive and update reviews were

published about oxidative stress in retinal cells in general and the relation to AMD by Jarrett *et al*[2] as well as about the blue light impact in the retina[4]. So we focussed more on the localization of blue light induced oxidative stress in retinal cells, especially in photoreceptors.

Here we want to show that photoreceptors are direct sources of oxidative stress after blue light impingement-especially their outer segments, in addition to the commonly known sites of radical production (mitochondria, chromophores and photosensitizers like lipofuscin). This is due to complex metabolic machinery in the outer segments where ectopic enzymes of the respiratory chain are located - besides the commonly known sources like NADPH-oxidases (NOX) and the visual pigments and their metabolites.

THE PHOTORECEPTORS AND THEIR SURROUNDINGS AS POSSIBLE SITES OF RADICAL PRODUCTION

Compared to other cell types of the retina, some features render the photoreceptors most vulnerable to oxidative damage. The photopigment rhodopsin is located within the outer segment discs. This rhodopsin undergoes photochemical processes, which lead to intermediates producing radicals a fact which is shown by the protein RPE65 (regeneration cycle protein of rhodopsin): without RPE65 blue light is much less dangerous for the retina[5]. Rhodopsin regeneration can also be halted by halothane, which renders the retina relatively insensitive to blue light[6].

Also secondary sources for radicals exist in the outer segments of the photoreceptors: high amounts of polyunsaturated fatty acids, which are especially prone to oxidation and carboxyethylpyrrol-modified proteins (CEP). These derivates of the non enzymatic oxidation of docosahexanoid acid originate during radical impact, molecules that are believed to be very harmful because these adducts can cause neovascularisation in tiny concentrations and independent from the VEGF pathway[7]. All these lipid and protein oxidation products deposit near Bruch's membrane and in Drusen below the RPE. Furthermore, these CEP proteins and other derivates of this kind are antigenic[8].

Normally, an over boarding accumulation of such waste products is prevented by constant renewal of the outer segment discs (around 10 of the many 100 discs per day)-means about 3 billion times disc shedding till an age of 70 years[9-11].

Oxidation of the disc membranes is also driven by the enormously high pO2 coming from the choroid-a region, which was previously thought to be "overperfused"[12-14]. However, in more pathologic states also zones of choroidal hypoxia can exist. Mostly, zones of wet-AMD-choroidal neovascularisation are located in areas of poor choroidal perfusion[13,14]. In non-exudative AMD, too the average choroidal flow is lower[15].

Even more important than the absolute oxygen partial pressure (pO2) in the choroid is the pO2 gradient also under physiological conditions. In their review, Stefánsson *et al*[14] report that under physiologic conditions "the pO2 decreases almost linearly with the distance from the choro capillaries to the inner portion of the photoreceptors". Interestingly, at the inner portion of the photoreceptors, the pO2 can reach 0 mmHg in the dark and is a little higher in the light. Hindrances in the diffusion through Bruch´s membrane (see above) will even lower this pO2 at the inner segment of the photoreceptor. At its outermost part (the ellipsoid), is the location of the photoreceptor mitochondria. This location, nearest possible to the pO2 source, is typical for the mitochondria that are moving actively to this location in many cell types[16].

BLUE LIGHT STRESS IN THE RETINA

The term light (or blue light-) stress of the retina is a multifaceted one: One should discern between (1) high intensity short-term damage (till 10 s): this means that the energy which impinges the retina is higher than the thermal diffusion (burning of the retina and especially of the RPE); and (2) low-dosage long-term effects (10 s and longer - till decades in human eyes).

For AMD pathogenesis Lawwill *et al*[17] demonstrated in 1977 that also low irradiation intensities of short wave length light could induce significant quantities of radicals-here, a cumulative retinal damage takes place during this kind of irradiation. Such low threshold blue light (may also be fractionated) can lead to accumulation of dangerous oxidation products also with the previously mentioned secondary oxidative reactions[17-19].

Regarding the whole eye, the cornea absorbs the UV - fraction of the light, the lens absorbs also wavelengths above 380 nm till around 400 nm. In elderly persons, the lens can absorb even wavelengths higher than 450 nm. This means the lens has a yellow till brownish colour-filtering out parts of the blue spectrum[20-22].

Besides the regulation *via* the pupil, the sensitivity of the eye is adjusted by regulation of the amount photopigment within the photoreceptors. More sensitive photopigment is located in the disc membranes under low light than if it is adapted to bright light. In addition to this, a feedback control *via* the horizontal cells exists[23]. If the spectrum is not continuous and shows only a few peaks, *e.g.*, in strip lamp light the eye adjusts to the irradiation energy, which is integral to the peaks (which is less than in a continuous spectrum at the level of the peaks). Thus, the eye increases its sensitivity and gets more vulnerable especially to the harmful wavelengths (blue peak). Many experimental studies prove the capability of the photoreceptors to adapt by the mechanisms mentioned above. Indeed, animals reared in dark have more photopigment than those reared under a normal day-night cycle [18,24-28].

ROS DAMAGE IN THE MACULA

The photoreceptors of the macula are exposed directly

to the light-no other cell layers are covering the photoreceptors and are absorbing parts of the light spectrum *via* cytochromes or other cell pigments[29].

Within the photoreceptors of the macula, the antioxidative molecules lutein and zeaxanthin filter out blue light due to their yellow colour as natural "sunglasses". These (also antioxidative) molecules are concentrated here thousand fold compared to other regions of the retina. The presence of lutein in this domain is also consistent with the proposed role of carotenoids in energy dissipation: in post-mortem human macula and retinal pigment epithelium a significant singlet oxygen scavenging capacity was found, which was based on these carotenoids[30]. Furthermore, Woo *et al*[31] could show experimentally that lutein itself has a great neuroprotective potential.

COMBINATION OF BLUE LIGHT STRESS AND ROS DAMAGE

A hint for the close connection of blue light stress and ROS production in the RPE comes from the observation that blue light toxicity is much higher under oxygenation levels near 100%-a situation found in vicinity to the choroid[32].

Another factor is the wavelength of light: In contrast to green light, blue light only hardly regenerates the rhodopsin molecule, thus intermediates accumulate and produce again ROS, superoxide radicals, hydrogen peroxide, hydroxyl radicals and other free radicals[12,33-40].

MITOCHONDRIA AS SOURCES OF ROS

The photoreceptors need even more energy than neurons and under aerobic conditions this energy is delivered by mitochondria[41,42]. Blue light and oxidative stress can elicit extra radical production by the respiratory chain handling with free electrons[43]. As a consequence of the radical stress coming from the mitochondria also other cell organelles are under thread including the nucleus and the DNA[44].

In the photoreceptors the mitochondria are most numerous in the "ellipsoid" of the inner segment-directly beneath the cilium that connects the inner segment with the outer segment forming a very small channel where the membranes, proteins and also ATP, pyruvate and other energy sources have to pass to the outer segments. However, one should keep in mind that the outer segment discs membranes consume a lot of energy, too.

In addition to mitochondria, numerous other radical sources are present in the cell, *e.g.*, membrane bound NADH and NADPH oxidases, so the impact of oxidative stress can elicit enhanced ROS production from different sites.

EFFECT OF BLUE LIGHT ON MITOCHONDRIA

Experimental studies show that blue light impact enhanced radical production especially in mitochondria. Enzymes of the respiratory chain absorb wavelengths between 440 and 450 nm producing radicals subsequently[45]. Inhibiting the respiratory chain by enzyme blockers or application of antioxidants reduces ROS formation and cell death[46].

The high amount mitochondria within the photoreceptors are sources of radical production and indeed, blue light elicits radical production there[47]. Also the radicals originating in the rhodopsin cycle in the outer segments produce di-retinoid-pyridinium-ethanolamine (A2E)-the most hazardous component of lipofuscin first found within the retinal pigment epithelium (RPE) and later within the Drusen[48-50]. Interestingly, A2E blocks cytochrome c oxidase within the mitochondria[51]. So the radical product A2E itself is blocking the respiratory chain and leads (as vicious cycle) to an increased deviation of electrons producing again new ROS.

ECTOPIC ENZYMES OF THE RESPIRATORY CHAIN WITHIN THE OUTER SEGMENTS

Panfoli *et al*[52-54] were the first authors who published the discovery that the outer segments discs harbour ectopic enzymes of the respiratory chain. The activity of these enzymes was in a range comparable to that of the respiratory enzymes in mitochondria. Panfoli *et al*[52-54] could also confirm the high proton gradient between outer and inner compartment of the discs. This is an important analogy because, *e.g.*, rods possess a double space encircled by membranes like the mitochondria do. Regarding the highly energy consuming process of phototransduction and the rapid increase of energy demand in light and dark cycles. Calzia *et al*[55] argue that it would be doubtful that ATP and phosphocreatine can diffuse from the inner segment (mitochondria!) to the outer third of the outer segments (only these are active in the rhodopsin cycle) with a proper timing[56]. Overall the O_2 consumption of the outer segments is three-fold greater than the inner retina[57]. The above mentioned paper of the Panfoli group[55] show even evidences that parts of the respiratory complexes come from mitochondrial membranes fused with the newly formed membranes of the outer segment discs.

Interestingly, we could show in our recent paper using a mouse explant model[58] that dyes that mark double membranes separating high proton gradients (like it was thought to be exclusively the case in mitochondria) and thus stain exclusively mitochondria, mark the outer segment of photoreceptors, too[58].

In this paper, we have also studied the ROS production (localisation and amount) in photoreceptors of retinal explants after blue light. We were surprised that the same amounts or even more of ROS were produced in the outer segments compared to the inner segments. Possibly, this ROS production in the outer segments is due to the newly found respiratory complex activity (see

above) or alternatively also due to NOX[59]-this is still to determine.

In the light of the present results, the energy delivery for the process of constant disc renewal should be therefore the predominant function of the inner segment mitochondria because shedding of outer segment membrane discs is prone to interference by blue light and ROS and this function requires a vast amount of energy (see above). The results of our recent study also suggest that not only the respiratory complexes of the mitochondria in the inner segment but also of the outer segments should be responsible for this very high oxygen consumption seen in the outer retina[58]. Impairment of the metabolic machinery (*e.g.*, lower pH) means also an inefficient photo transduction, which could be demonstrated by Calzia *et al*[60].

On the other hand, the high vulnerability of the outer segments to ROS damage could also lead morphologically to disorganisation of the photoreceptor outer segments[61]. In this regard we could demonstrate in a previous paper[61] that, indeed, after blue light and enhanced ROS production the alignment of the outer segments and the disc arrangement is disturbed, long before the photoreceptors go into degeneration and apoptosis. This finding corroborates a hypothesis of Eckmiller[62] that explains why this disturbed alignment of photoreceptors and other retinal cells along the visual pathway are responsible for the distortions of the central visual field in early AMD[63] patients.

CONCLUSION

The review of the literature and the new results of the Panfoli group and of our group show how complex the pathogenesis is during the early stages of AMD. This also suggests that clinicians should look especially to the macular photoreceptors, to the alignment of outer segments with more refined methods. What is also needed is the development of high resolution functional imaging of the metabolic state in the different retinal layers because only the very late stages of AMD can be monitored and treated till now. Such refined imaging methods would also allow monitoring of the impact of dietary[58] and life style changes on the progression of early AMD.

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Choroidal neovascularization secondary to pathological myopia

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Core tip: Myopic choroidal neovascularization is one of the leading causes of visual impairment worldwide, with increasing significance in Asia. Previous treatments aimed to maintain vision; however, new treatments such as vascular endothelial growth factor inhibitors have been shown to restore vision. However, their long term efficacy and safety is still unknown.

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Abstract

Myopic choroidal neovascularization (mCNV), one of the complications of pathological myopia, is also one of the leading causes of visual impairment worldwide. The socioeconomic impact of mCNV in Asian countries is particularly significant due to the rising incidence of pathological myopia. There have been major advances in the treatment of mCNV in the past few years. Previous treatment modalities, such as thermal laser photocoagulation and photodynamic therapy, aimed to prevent vision loss; however, newer modalities such as intravitreal anti-vascular endothelial growth factor (VEGF) agents have been shown to successfully restore vision in many patients. Challenges remain as long term safety and efficacy of anti-VEGF agents are unknown. This article aims to provide a review of the literature of the epidemiology, progression, clinical course and treatment modalities as well as areas of future developments related to myopic CNV.

INTRODUCTION

Pathological myopia is characterized by the excessive elongation of the globe and progressive degenerative changes and is a major cause of visual loss worldwide. The abnormal elongation of the eyeball in pathological myopia is associated with a spectrum of anatomical changes of the posterior pole, such as posterior staphyloma, atrophy of the retinal pigment epithelium (RPE), Bruch's membrane cracks, subretinal hemorrhage, retinal detachment and choroidal neovascularization (CNV). Indeed, myopic CNV (mCNV) is one of the most vision threatening complications in pathological myopia[1]. It has been estimated that mCNV develops in 5%-11% of individuals with pathological myopia[2,3]. Affected individuals are often young and in their working life. The public health impact and socioeconomic cost associated with mCNV is therefore substantial.

There have been major advances in the treatment of

mCNV in the past few years. Treatment modalities have evolved from thermal laser photocoagulation and photodynamic therapy, which aim to prevent vision loss, to the use of intravitreal anti-vascular endothelial growth factor (VEGF) agents, which have been shown to successfully restore vision in many patients. However, challenges to maintain long term vision remain, from the risk of recurrence and development of chorioretinal atrophy around the regressed CNV.

This article aims to provide a review of the literature of the epidemiology, progression, clinical course and treatment modalities as well as areas of future developments related to myopic CNV.

Definition of pathological myopia

There is currently no consensus on the definition of pathological myopia. Commonly used criteria for defining pathological myopic include refractive error and biometric criteria. In addition, clinical features commonly associated with pathological myopia, such as the presence of staphyloma and fundus changes such as lacquer cracks and chorioretinal atrophy, are often used[4,5]. In previously published population studies, a range of criteria have been used, such as refractive errors of -5 to -10 D and axial lengths of at least 25.0 mm to 26.5 mm. For example, the Blue Mountains Eye study, the Handan Study and the Hisayama study based their definition of high myopia on a refractive error of -5.0 D and worse. The Singapore Epidemiology of Eye disease program and the Shihpai study used a more stringent criterion of refractive error of -6.0 D and worse[6,7].

Epidemiology of myopia

The reported prevalence of pathological myopia based on population studies is estimated to be between 2% to 10% among adults aged 40 years and above[3,8-12]. There is a significant variation in the prevalence of high myopia between populations and East Asian countries have reported a significantly higher prevalence of high myopia compared to the rest of the world[13]. The overall prevalence of myopia also appears to be increasing, thus reflecting a complex interplay of genetic, environmental and epigenetic factors underlying the pathogenesis of this condition[2]. A predominantly Caucasian population in the United States, western Europe and Australia reported the prevalence of myopia (< -5 D) as 4.5%[14], compared to the Hisayama study in Japan which reported a higher prevalence of 5.7%[15]. In the Singapore Eye Study, the population prevalence was reported as 4.0%[6]. However, there was a significant difference between ethnic groups, with the prevalence among Chinese participants (6.1%)[9] 2-hold higher than that in Malay (3.0%)[8] and Indian participants (2.8%)[6]. Correspondingly, the impact of myopia is significantly higher in countries with a higher prevalence. In Japan, pathological myopia is the leading cause of blindness and in the Chinese population it has been reported to be the second commonest cause of blindness[7,16-18]. A recent systematic review reported the prevalence of pathological myopia to be 0.9%-3.1%. The prevalence of visual impairment attributable to pathological myopia was reported to range from 0.1%-0.5% in European studies and from 0.2%-1.4% in Asian studies[3].

Long term progression of myopic maculopathy

The myopic fundus has several clinical changes that may contribute to visual loss. However, it has been shown that these changes are not common in young myopes[19]. A study of myopia related changes in Singapore revealed that posterior staphyloma was the most common form of myopic macular change (23%), followed by chorioretinal atrophy (19.3%) in high myopes (< -6 D) over the age of 40[20]. These features increased in prevalence with increasing age, myopic refraction and axial length. Furthermore, long term follow-up of eyes with myopic maculopathy demonstrated that progression of lesions developed in a significant proportion[7,15,17,21,22]. Among individuals with retinal changes related to high myopia, it is estimated that 10% will develop CNV over 10 years[2,23]. However, a clear understanding of the relationship between the severity of myopia and the progression to sight threatening consequences remains elusive. One such theory suggests a linear relationship between the increased risks of pathology with each increase in spherical equivalent in diopters or axial length. Another theory suggests that there could be a threshold effect and the risk of pathology increases exponentially beyond a level of refractive error[24]. The thinning of the choroid and progressive stretching of the retina leading to choroidal ischemia and RPE atrophy may contribute towards the eventual formation of mCNV. Lacquer crack, which results from breaks in the Bruch's membrane, is also considered a main predisposing factor for the formation of neovascularization.

CNV secondary to pathological myopia

Myopia is the most common cause of CNV in individuals below the age of 50[25]. mCNV is also the second most common cause of CNV following age-related macular degeneration, constituting 5%-10% of all CNV[12]. Sequelae of mCNV[3] include macular atrophy and scarring, which are major causes of visual loss in the long term[22,26-28]. The overall prevalence of mCNV is estimated to be 0.04% to 0.05% in the general population[2]. In pathological myopes, however, the incidence and prevalence have been reported to be as high as 10% and 0.5% respectively[29] and bilateral in 15%[3]. The risk of developing mCNV has been reported to increase with increasing severity of myopia[29,30] and macular changes, such as tessellated fundi, lacquer cracks, diffuse atrophy and patchy atrophy[23,31,32].

Clinical characteristics

CNV secondary to pathological myopia exhibits significant differences in clinical characteristics when compared to CNV secondary to age-related macular degeneration (AMD). Patients with mCNV often present earlier with better visual acuity. They may report subtle visual symptoms such as metamorphopsia and central scotoma[28].

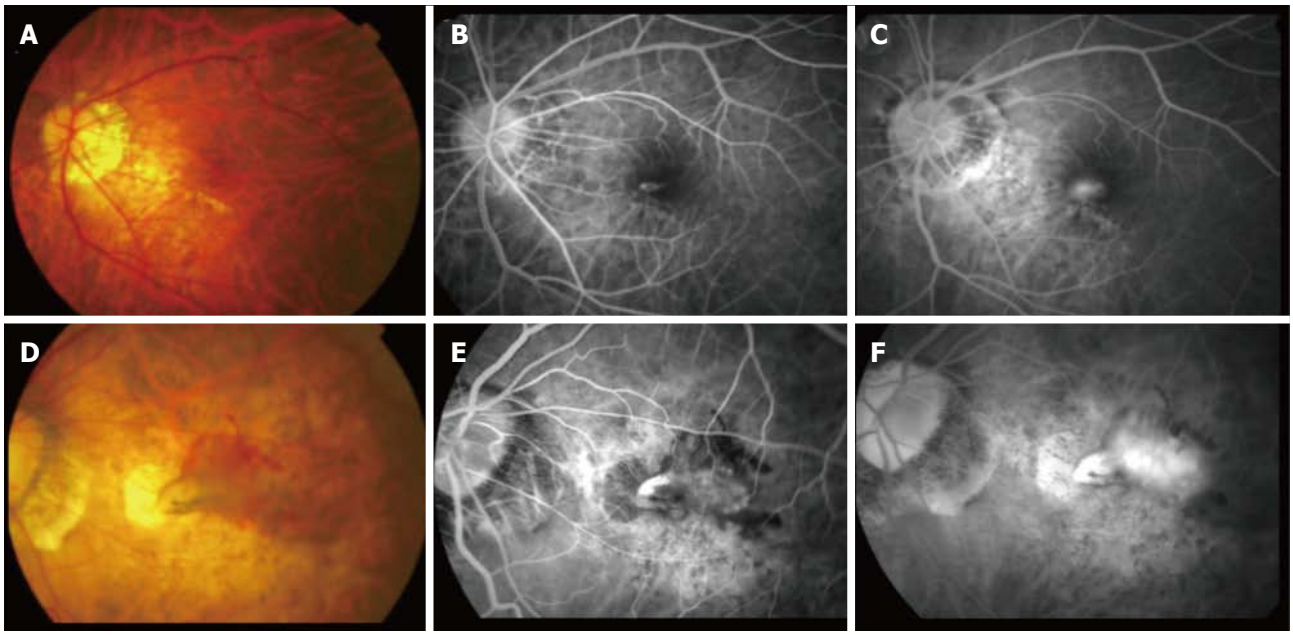

Figure 1 Clinical features of a typical choroidal neovascularization secondary to pathological myopia. (A) Color fundus photography and corresponding fluorescein angiography (FA) (B and C) showing a younger patient with a small choroidal neovascularization lesion adjacent to the lacquer crack compared to (D) color fundus photograph and corresponding FA (E and F) showing an older patient with a much larger lesion with significant intraretinal fluid and extensive background atrophic changes.

On clinical examination, the CNV typically appears as a grayish membrane with or without retinal hemorrhages. The tessellated fundus often makes determination of retinal swelling challenging. In addition, the amount of intraretinal and subretinal fluid that accompanies the mCNV is often less than that seen in CNVs secondary to AMD. A more effective pump mechanism in the retinal pigment epithelium in these eyes, especially in younger patients, has been postulated as a potential explanation of this difference. The minimal exudation is postulated to be due to the attenuated nature of the choroidal blood circulation in the pathological myopic fundus[33]. In an older patient, however, the clinical features tend to show more overlapping features with CNVs secondary to AMD (Figure 1). These eyes often have larger lesions and more exudative changes and may eventually lead to the formation of disciform scars[27]. If the underlying etiology of the CNV is not clear, the presence of myopic changes in the fundus, such as the presence of staphyloma, lacquer crack and peripapillary atrophy, may help distinguish a mCNV from AMD. In addition, type I CNVs, which are the most common type in AMD, are relatively uncommon in pathological myopia[34,35].

DIAGNOSTIC CHARACTERISTICS

Optical coherence tomography

Optical coherence tomography (OCT) is a non-invasive imaging modality, which provides an *in vivo* cross section tomograph of the retina. It provides valuable information regarding the localization, character and activity of CNV.

Myopic CNV typically appears as a hyperreflective lesion above the reflective band corresponding to the retinal pigment epithelium (RPE). Intraretinal fluid and disruption of the retinal layers often accompany the hyperreflective lesion. However, the amount of intraretinal or subretinal fluid may vary. In younger patients with small mCNV there may be relatively limited surrounding intraretinal fluid and the contour of the internal limiting membrane may be minimally altered in some of these cases. As the lesion becomes less active, OCT can be used to monitor the decrease in the size of the lesion. The outline of the lesion also becomes increasingly distinct and exhibits high reflectivity. Correspondingly, the amount of intraretinal fluid surrounding the lesion can be seen to decrease progressively as activity decreases (Figure 2)[34].

In addition to demonstrating the mCNV lesion, other myopia-related morphological changes are often seen on OCT. These include the presence of staphyloma and a relatively thin choroid. In addition, other co-existing pathologies, such as epiretinal membrane and retinoschisis can also be documented.

There are, however, some limitations in the use of OCT, especially in highly myopic eyes. The image resolution may be affected by optical factors in the presence of very long axial length and posterior staphyloma. The accuracy of quantitative data, such as central macular thickness measurement, in highly myopic eyes can be variable due to distortion in highly elongated eyes and the lack of normative data. Recently, Keane *et al*[36] developed software that attempts to improve the accuracy of retinal thickness measurement and may be helpful in the outcomes of treatment.

The ability of using enhanced depth imaging (EDI)-

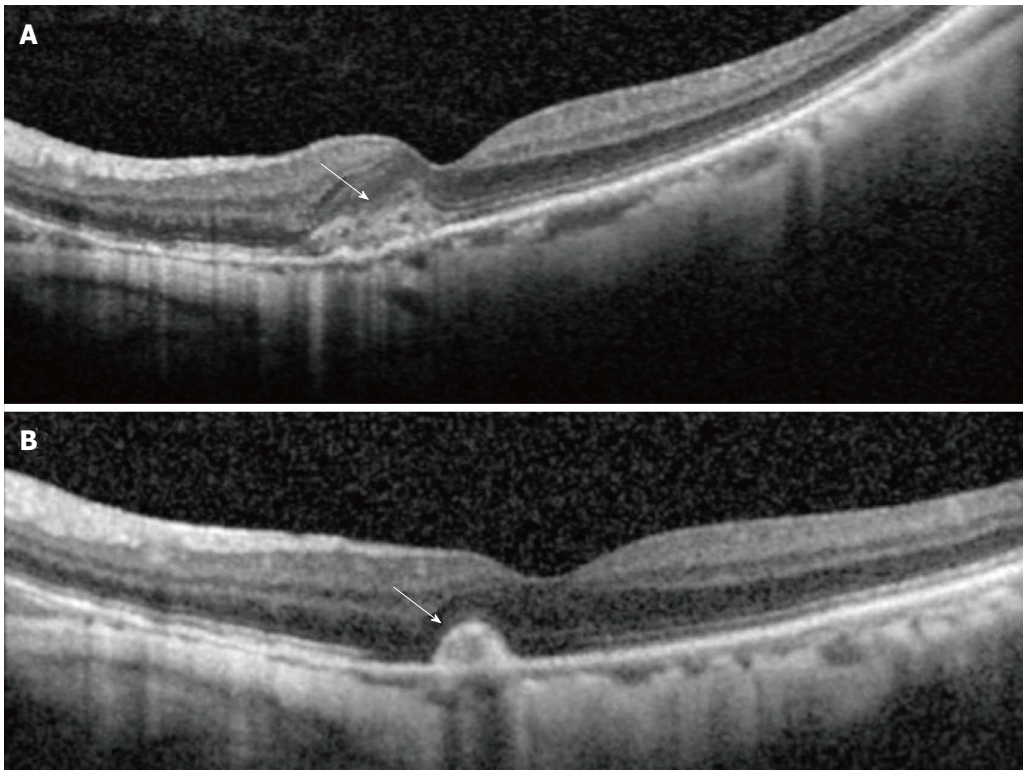

Figure 2 Optical coherence tomography showing corresponding changes in activity. (A) Shows hyperreflective lesion corresponding to a small juxtafoveal myopic choroidal neovascularization (arrow) located above the retinal pigment epithelial cell layer with minimal exudation. After 3 mo (B), the lesion had scarred up, represented by a highly reflective lesion with sharp outline, and no intraretinal fluid is seen, which suggests an inactive lesion (arrow).

OCT techniques to image choroidal thickness has led to considerable interest in studying the role of the choroid in the pathogenesis of mCNV[37-39]. It has been shown that choroidal thickness decreases with age and myopia. Several studies have suggested that reduced choroidal thickness along with the presence of lacquer cracks and posterior staphylomas are significant risk factors for developing myopic CNV[40-43]. In addition, regional variations in choroidal thickness have also been shown. This thinning of the retina and choroid coupled with age related retinal-choroidal attenuation leads to a loss in choroidal vasculature, which is unable to meet the oxygen demands of the retina, and predisposes these eyes to developing myopic related retinal dysfunction[44]. Using 3-dimensional reconstruction, other authors have demonstrated that the edge of staphyloma may contribute towards a dome-shaped macula appearance described in some eyes[45].

Fundus fluorescein angiography

Although OCT provides valuable information for follow-up, fundus fluorescein angiography (FA) remains the gold standard for the confirmation of any CNV lesion at baseline. FA is also more sensitive in detecting mild activity from leakage in cases where OCT shows questionable presence of intraretinal fluid. The lesions typically display a classic pattern of leakage, in keeping with a type 2 CNV[46]. It is important to distinguish a subfoveal mCNV from a juxtafoveal or extrafoveal mCNV as the location of the lesion has been found to be an important prognostic factor. In addition, the amount of leakage on FFA is a good indicator of the level of activity of the lesion, which is an important factor in determining treatment options for the disease.

Indocyanine green angiography

As most mCVN lesions are type 2 CNV, FA and OCT provide adequate information in most cases. However, ICGA may provide additional information in selected cases, particularly where masking from blood might obscure visualization of the CNV on FA. A simple bleed associated with lacquer crack without CNV, or Fuchs' hemorrhage, can be distinguished from mCNV on ICGA findings. Abnormal vasculature or a hyperfluorescence on ICGA may indicate the presence of CNV when information from FA is limited due to masking by blood. In Fuchs' hemorrhage, however, no abnormalities of the choroidal vasculature will be seen on ICGA[47]. ICGA can also be used to detect and characterize lacquer cracks, which appear as linear hypofluorescent streaks in late phase ICGA[48].

Treatment options for myopic CNV

Over the last decade, various treatment options for mCNV have been proposed, including thermal laser photocoagulation, photodynamic therapy and submacular surgery. The success rate of these treatment modalities was variable. With the success of anti-vascular endothe-

lial growth factors (VEGF) described in the treatment of CNV secondary to AMD, there have been many cases series published advocating their use for mCNV as an off label option. Recently, the results of two large clinical trials using anti-VEGF therapy in mCNV have been released, both of which reported very favorable results.

Thermal laser photocoagulation

Thermal laser photocoagulation and surgery no longer constitute the mainstay of treatment for myopic CNV. This is due to the irreversible scarring, central scotoma and high rates of recurrence.

For many years, laser thermal photocoagulation was the only modality for treating mCNV. Due to the immediate severe reduction in vision and central scotoma, laser thermal photocoagulation was limited to extrafoveal lesions. However, even in these cases, the long term efficacy is limited by atrophic scar creep and the high rate of recurrence[49].

Surgery

Myopic CNV, which is predominately a type 2 CNV, theoretically can be excised surgically as it is located anterior to the RPE and hence can be removed with relative preservation of the RPE layer. However, surgical excision of subfoveal myopic CNV has had disappointing results due to post-operative atrophic scar formation, central scotoma and a high rate of recurrences[50-52]. With less invasive therapies available, surgical excision is no longer a viable option.

Other surgical techniques such as macular translocation (MT) have been proposed. The benefits stem from the displacement of the neurosensory retina at the fovea to an area that has a presumed healthier RPE-Bruch's complex together with the conversion of a subfoveal to an extrafoveal lesion which also allows for treatment modalities that might otherwise harm the fovea[53]. The clinical efficacy of such procedures is variable and limited to reports from case series[54-56].

Photodynamic therapy

The efficacy and safety of PDT in mCNV lesions was studied in the verteporfin randomized, double masked, placebo-controlled clinical trial[57]. The VIP study demonstrated a stabilization of visual acuity in 72% of eyes with subfoveal CNV following PDT over a period of 12 mo. However, there was still a mean loss of visual acuity of 2.8 letters at month 12. At month 24, the initial stabilization was not maintained. These findings are complemented by several smaller case series also showing benefit in visual stabilization during the early phase[57-60]. Based on the VIP study, PDT was approved for treating subfoveal mCNV.

Anti-VEGF treatment

The efficacy of anti-vascular endothelial growth factor (anti-VEGF) therapy has already been demonstrated in CNV secondary to AMD, diabetic macula edema and macular edema secondary to retinal vein occlusion. Favorable results of anti-VEGF therapy in mCNV have been reported in a series of mostly non-randomized, uncontrolled studies. Rapid gain of vision of 10-15 letters within an average of 1 to 3 injections over a 12 mo period has previously been reported[61-66].

The REPAIR study is a phase 2, open-label, single arm study which investigated the efficacy of intravitreal ranibizumab in mCNV. After a single ranibizumab injection at baseline, patients were retreated on a pro re nata (PRN) basis. At month 5, the mean best corrected visual acuity (BCVA) improved by 12.2 letters compared to baseline. The mean number of retreatments was 1.9 injections up to month 6[67].

The strongest evidence for the beneficial effects of anti-VEGF therapy in the treatment of mCNV comes from two recently completed phase Ⅲ clinical trials; the Ranibizumab and PDT (verteporfin) evaluation in myopic choroidal neovascularization (RADIANCE) trial and the VEGF Trap-Eye in Choroidal Neovascularization Secondary to Pathological Myopia (MYRROR) Study.

The RADIANCE trial was a phase Ⅲ, 12 mo, randomized, double-masked, multi-center, active-controlled study which compared the efficacy and safety of ranibizumab 0.5 mg against verteporfin photodynamic therapy (vPDT) in 277 patients with myopic CNV. This study demonstrated that ranibizumab treatment provided superior best-corrected visual acuity (BCVA) gains (10 ETDRS letters) *vs* vPDT (2.2 ETDRS letters) at 3 mo. The secondary outcome showed that ranibizumab treatment guided by disease activity criteria (2.5 injections) was non-inferior to VA stabilization criteria (3.5 injections) up to month 6. Over 12 mo, individualized ranibizumab treatment was effective in improving and sustaining BCVA and was generally well tolerated in patients with myopic CNV. The anatomical outcomes of this study were consistent with the gains in BCVA. There was a reduction in the proportion of patients with subretinal fluid, intraretinal edema and/or intraretinal cysts from baseline to 1 year, with a median of 3.5 injections in the disease activity criteria group and 4.6 injections in the VA stabilization group[68].

The MYRROR study was a multicenter, randomized, double-masked, sham-controlled trial which assessed the efficacy and safety of intravitreal administration of aflibercept (VEGF Trap-Eye; Eylea)[69]. The study was conducted in 20 sites across 5 Asian countries between 2010 and 2013. Patients were randomized in a 3:1 (aflibercept: sham injections) and followed up for 24 wk. Patients in the active treatment arm received one initial 2 mg dose of aflibercept. Patients were subsequently evaluated every 4 wk and received additional aflibercept injections determined by visual and anatomical criteria, through 20 wk. Patients on the sham arm received monthly sham injections through week 20. Starting at week 24, patients in both arms were eligible to receive aflibercept injections on an as needed basis through week 48. At 24 wk, the aflibercept group gained 12.1 ETDRS letters, which was

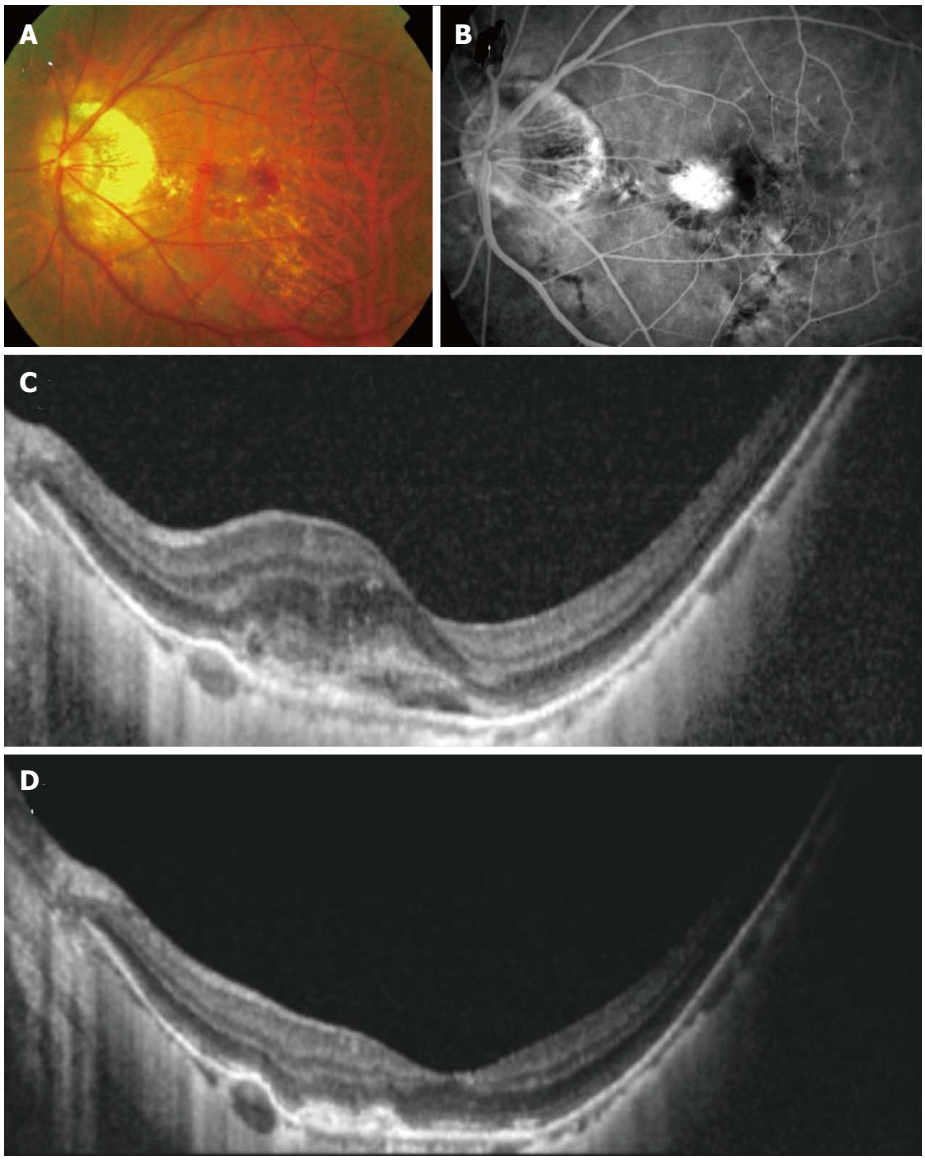

Figure 3 Resolution seen with anti-vascular endothelial growth factor treatment in myopic. Choroidal neovascularization (CNV) color fundus photograph (A), fluorescein angiography (FA) (B) and optical coherence tomography (OCT) (C) showing a larger juxtafoveal myopic CNV with significant amount of intraretinal fluid. Note the lacquer cracks which are clearly visible on the FA. After a course of intravitreal bevacizumab, OCT demonstrated resolution of intraretinal fluid and consolidation of the CNV (D).

significantly better than the sham injection group, which experienced a 2 letters loss. The efficacy gains at week 24 in the treatment arm extended further until week 48. Patients in the treatment group received a median of 2 injections in the first quarter of the study (baseline to week 12). In each of the following three quarters, the median of injections was 0.

These results support the efficacy of anti-VEGF therapy in mCNV (Figure 3). However, there are currently no randomized controlled trials on the use of other anti-VEGF agents, such as bevacizumab, in mCNV. Neither are there high quality head-to-head comparison studies to examine whether there may be difference in the efficacy and safety between different anti-VEGF agents. A retrospective study by Lai *et al*[70], however, shows promising results in the long term efficacy of both bevacizumab or ranibizumab as primary treatment for subfoveal mCNV where visual gains and number of retreatments appeared to be similar between bevacizumab and ranibizumab.

TREATMENT REGIMENS

Loading regimen

A 3 monthly injection (loading phase) is often practiced in anti-VEGF therapy in AMD. However, current evidence suggests this may not be necessary in mCNV. Indeed, the VEGF load in mCNV has been suggested to be lower than that in AMD[71]. A series of uncontrolled studies have reported favorable results using a pro re nata (PRN) regimen. Iacono *et al*[72] demonstrated favorable outcomes with stabilization of vision and > 90% closure of CNV with the use of bevacizumab on an as-needed

basis with an average of 4.74 injections in the first year. Wakabayashi *et al*[73] compared a PRN regimen with a 3 monthly followed by PRN regimen and concluded that there was similar visual outcome over 12 mo with fewer injections in the group without initial loading[73]. Neither the RADIANCE nor MYRROR studies mandated an initial loading phase and reported low (< 3) mean and median number of injections up to month 6 and week 24 respectively.

Follow-up regimen

Both the RADIANCE and MYRROR studies followed-up participants on a monthly basis. However, this may be challenging in the clinical setting. In the case of AMD, various modifications to allow longer follow-up have been studied in trials such as the efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration (EXCITE study), Prospective OCT Study With Lucentis for Neovascular AMD (PrONTO study) and treatment-and-extend regimen[74-77]. In mCNV, however, there are currently no published data in this respect.

Retreatment

The assessment of treatment response and decision of when to stop treatment is based on multiple factors, including visual acuity, symptomatology, clinical assessment and imaging results. Common regimens include "treat to dry" based on OCT assessment and "treat to stable vision" based on visual acuity. In the RADIANCE study, two dosing regimens were compared. In the visual acuity stabilization group, dosing was stopped if there was no change in BCVA compared to 2 preceding monthly visits. In the disease activity group, dosing was stopped if there was no disease activity based on vision impairment attributable to intra or subretinal fluid or active leakage. The study reported that ranibizumab treatment driven by disease activity showed non-inferiority to treatment driven by stabilization criteria, with respect to mean BCVA from baseline to month 6, gaining 11.7 and 11.9 letters respectively. The corresponding number of injections was 2.5 in the disease activity group and 3.5 in the stabilization group.

Safety of anti-VEGF therapy

The systemic safety of anti-VEGF has been questioned and remains a possible concern[78-80]. The pivotal clinical trials of ranibizumab and aflibercept in AMD did not show a significant increase in stroke risk or thrombotic events[81-83]. However, a pooled analysis of five randomized controlled trials using ranibizumab suggested that patients with a history of previous stroke may be at increased risk of developing stoke after anti-VEGF therapy[84]. It is also unclear whether the anti-VEGF agents differ significantly with respect to safety. Carneiro *et al*[85] reported that VEGF plasma levels decreased 42% in patients treated by intraocular injection of bevacizumab but not in ranibizumab-treated patients, potentially highlighting the safety profile between the two drugs[85]. In a US Medicare study, higher risks of stroke and all-cause mortality were observed with intravitreal bevacizumab compared with ranibizumab[86]. Furthermore, there are potentially additional ocular specific complications in highly myopic eyes. Worsening of retinoschisis, macular hole and macular detachment have been described after intravitreal anti-VEGF for mCNV[87]. As seen in other treatment modalities, progression of chorioretinal atrophy around the mCNV has also been described following anti-VEGF therapy[26,88] (Figure 4). However, the proof of any causal relationship remains difficult with no clear evidence from clinical trials.

Monitoring of disease activity

FA remains the standard for diagnosis and disease activity monitoring of mCNV[89,90]. With the advent of anti-VEGF treatment, there is growing importance in the use of OCT as a simple non-invasive alternative of disease monitoring. There are, however, shortfalls of the use of OCT in disease monitoring of mCNV. In myopic eyes, the retina and choroids are thin and mCNV typically have minimal leakage with minimal intra/subretinal fluid; hence, OCT findings may not be as informative compared to its use in AMD CNV. Introni *et al*[91] suggest that there is no evidence for central retinal thickness or sub/intraretinal fluid in mCNV. Instead, they suggest the use of outer retinal characteristics on SD OCT: identification of a hyperreflective lesion with fuzzy borders and a more highly reflective core above the RPE, and "absent or altered" IS/OS junction as signs of activity, and they found a regression of these findings and RPE thickening after treatment[91].

Prognostic factors

Many studies have studied the prognostic factors for mCNV. Prognostic factors for visual outcome after anti-VEGF therapy include age, CNV size and location, baseline VA, presence of chorioretinal atrophy, choroidal thickness and recurrence of mCNV[92]. Other factors such as refractive error, axial length and lens status have been variably described. Furthermore, prior PDT has also been suggested to limit visual prognosis. In addition, age, CNV size, baseline choroidal thickness and the presence of lacquer cracks have been described as prognostic factors for needing a larger number of injections[93].

Age of onset of CNV: Younger patients generally obtained more favorable results than elderly subjects. In various studies, a significant improvement in vision was generally seen in younger patients (mean age 48-53) than studies enrolling older patients (mean age 60). This may be attributed to the age related deterioration of the RPE which decreases the inhibition of CNV growth. Elderly patients require more anti-VEGF injections compared to younger subjects. In addition, the younger subjects have a smaller area of pre-existing chorioretinal degeneration, resulting in the significant improvement in vision follow-

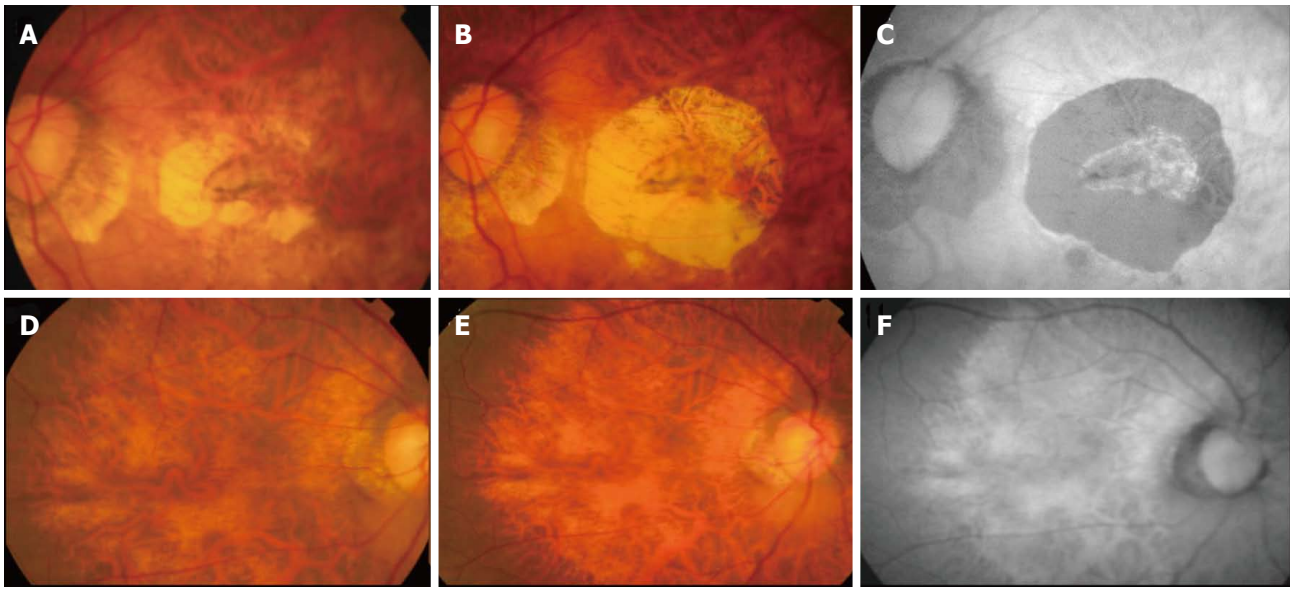

Figure 4 Progression of atrophy around treated choroidal neovascularization. Color fundus photograph (A) showing inactive choroidal neovascularization (CNV) after 1 year therapy with ranibizumab, color fundus photography (B) showing increase in CNV related chorioretinal atrophy two years later. No further therapy was given during the intervening period. Autofluorescence imaging (C) demonstrating clearly the area of retinal pigment epithelial atrophy as hypoautofluorescent area. The fellow eye showed diffuse atrophy but no significant progression was seen during the same follow-up period (D-F).

ing anti-VEGF treatment[72,94-96].

Location of CNV: Subjects with subfoveal CNV generally had a worse final VA compared to subjects with lesions that were non subfoveal. Hayashi *et al*[97] also showed that the incidence of chorioretinal atrophy in subfoveal CNV was 80% compared to 6% in non subfoveal CNV, with a significant difference in the size of chorioretinal atrophy[97].

Size of CNV: Nakanishi *et al*[95] showed that pre-treatment CNV size was significantly associated with both the BCVA and the change in the BCVA at 24 mo after the initial anti-VEGF therapy. Eyes with smaller mCNV had both better BCVA and better improvement of BCVA at 24 mo after the initial treatment than those with larger myopic CNV. Similar findings were reported for age-related macular degeneration (AMD) where the size of the CNV before PDT or anti-VEGF therapy was a predictive factor for the post-treatment BCVA. However, the mechanism of how the CNV lesion size influences the visual outcome after these treatments has not been determined[95].

Prior PDT: Several studies have performed sub group analysis of eye outcomes with anti-VEGF treatment with and without prior PDT treatment. Ruiz-Moreno *et al*[94] specifically studied the influence of PDT on visual outcomes in eyes with myopic CNV treated with intravitreal bevacizumab. These studies all show similar conclusions that prior treatment with PDT seems to adversely affect the BCVA outcome with additional anti-VEGF treatment. Poorer visual outcome in this group with prior PDT may due to several factors, including choroidal ischemia, damage to RPE and photoreceptors and choriocapillary atrophy[94,98].

Baseline vision: In a multivariate analysis of a retrospective, observational case series of 103 eyes of 89 consecutive patients with subfoveal myopic CNV by Yang *et al*[92], baseline BCVA, along with other factors such as choroidal thickness and CNV size, was associated significantly with poor final BCVA. This poor functional outcome in eyes with poorer baseline VA may just reflect the more aggressive CNV which would have a poor prognosis with any treatment modality[92].

Recurrence

Recurrence of mCNV is a well-recognized challenge. In the RADIANCE study, 19.0% to 29.1% of eyes continued to have CNV leakage on FA at month 12. In the disease activity group, 37.1% of eyes required additional injections according to retreatment criteria between month 6 and month 11[68]. In a retrospective observational case series of 103 eyes with mCNV, recurrence was reported in 23.3%. Most of the first recurrences (72.7%) occurred during the first year of follow-up. Baseline CNV size and the presence of lacquer cracks have been described as prognostic factors for recurrence[92].

CONCLUSION

Myopic CNV is one of the most common vision threatening complications of pathological myopia, with a significant socioeconomic impact as it affects a younger, working age group of patients compared to other common blinding diseases. The natural progression of mCNV shows an early stabilization of vision followed by

gradual decrease in VA over time due to the development of chorioretinal atrophy. The final visual outcome relates closely with the distance of CNV from the fovea and inversely with the size of CNV. Subfoveal location of CNV is associated with worse visual outcome when compared with a juxtafoveal and extrafoveal location; however, there is a high likelihood of conversion of these CNVs to subfoveal type or extension of the CNV within the fovea.

Currently, anti-VEGF treatment appears to be the most promising treatment modality for myopic CNV. Compared to previous treatment options like PDT which have been shown to only stabilize vision in the short term, there is now level 1 evidence to support the efficacy of specific anti-VEGF agents in mCNV with visual outcome superior to that achieved with PDT.

While these studies affirm anti-VEGF treatment for short term gains in vision, further research is still needed regarding the optimal follow-up interval, rate and risk of recurrence and late atrophy on treated eyes. In the long term, the development and enlargement of chorioretinal atrophy around regressed CNV remain the determining factors on final visual outcome. Hence, further research is necessary to investigate the underlying mechanisms of chorioretinal atrophy and to establish the best treatment modalities to prevent these late complications.

Other future directions of study would be to determine the risk factors associated with the development of myopic CNV in pathological myopic eyes. With newer imaging technologies available, such as swept source OCT, the state and health of the choroid in myopes can be better assessed. This can help in the understanding of the changes in retinal metabolic support in highly myopic patients and the role of choroidal abnormalities in the pathogenesis of myopic degenerative diseases.

In summary, myopic CNV remains a common cause of vision loss. With better understanding of the pathophysiology, risk factors and natural history, better therapies can be developed to both prevent and treat the disease.

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MINIREVIEWS

Glaucoma and Alzheimer's disease: Their clinical similarity and future therapeutic strategies for glaucoma

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Abstract

Glaucoma refers to a group of diseases characterized by optic neuropathies that are commonly associated with degeneration of the retinal ganglion cells. Although intraocular pressure (IOP) is the only proven treatable factor, several studies indicate that other factors are involved in the pathogenesis of glaucoma. Since normal tension glaucoma (NTG) is the most common glaucoma at least in Japan and South Korea, development of new therapeutic strategies for glaucoma, besides reduction of IOP, is crucial. The clinical characteristics and mechanisms underlying neuronal degeneration in Alzheimer's disease, a progressive neurodegenerative disease, are similar to those of glaucoma. Impaired cerebral blood flow (CBF) is common to both these diseases; therefore, improving CBF may be considered a new treatment for glaucoma, especially for NTG. In addition, targeting the formation and aggravation pathway for amyloid-β and administration of apolipoprotein E-containing lipoproteins may be potential strategies for glaucoma treatment.

Key words: Glaucoma; Alzheimer's disease; Retinal ganglion cells; Cerebral blood flow; Amyloid-β; Apolipoprotein E

Core tip: This review summarizes studies describing the similarities between glaucoma and Alzheimer's disease, thereby suggesting new probable therapeutic strategies for glaucoma.

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INTRODUCTION

Glaucoma refers to a group of diseases characterized by optic neuropathies that are commonly associated with degeneration of the retinal ganglion cells (RGCs)[1,2], which results in a characteristic optic nerve head (ONH) appearance and corresponding visual field defects. Global surveys indicate that glaucoma is the second leading cause of visual impairment, next to cataract[3]. Normal tension glaucoma (NTG) is the most common type of glaucoma at least in Japan and South Korea[4,5]. Currently, although intraocular pressure (IOP) is the only proven treatable factor for glaucoma, neuroprotection is increasingly being considered as a treatment strategy for glaucoma[6-8].

Alzheimer's disease (AD), a representative neurodegenerative disease, is one of the most common causes of dementia. Hallmarks of AD include extracellular amyloid-β plaques and intracellular neurofibrillary tangles comprising abnormally phosphorylated tau protein[9,10]. The ε4 allele of apolipoprotein E (APOE) has been found to be a major genetic risk factor for AD[11].

In this review, the association of glaucoma with AD is summarized; then, based on their common pathophysiology, probable therapies for glaucoma are presented

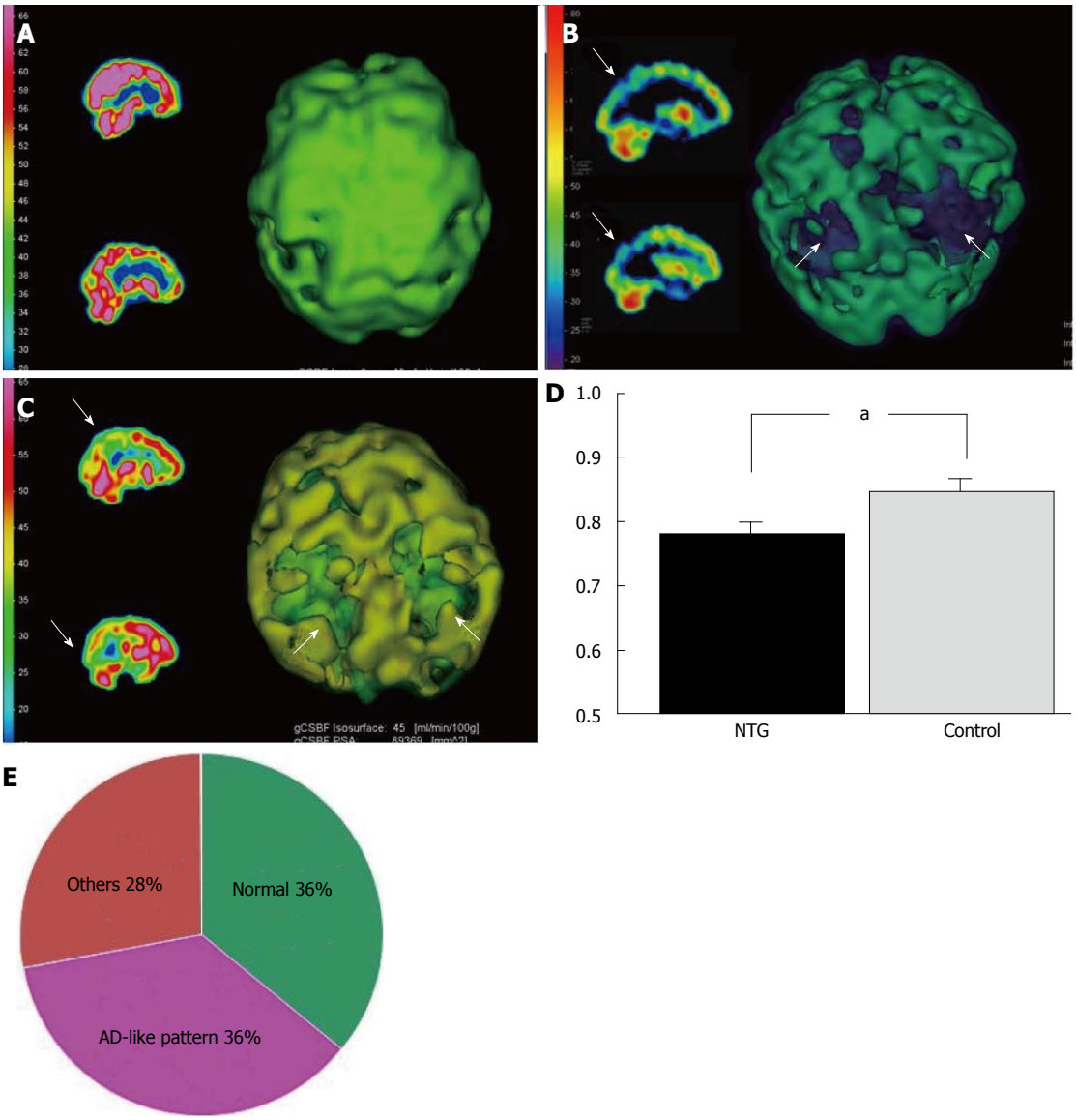

Figure 1 Representative examples of normal, Alzheimer's disease and Alzheimer's disease-like cerebral perfusion patterns by SPECT images (sagittal sections and 3D images). A: Normal pattern; B: AD pattern; C: AD-like pattern. Arrows indicate decreased CBF; D: Comparison of relative CBF in the parietal lobe between NTG patients and controls. [a]*P* = 0.02, paired t-test; E: Classification of cerebral perfusion patterns by SPECT images in 64 patients with NTG. AD: Alzheimer's disease; NTG: Normal tension glaucoma; CBF: Cerebral blood flow.

briefly.

ASSOCIATION OF GLAUCOMA WITH AD

Several reports have documented the clinical association of glaucoma with AD. Bayer *et al*[12] showed that patients with AD may have a significantly increased incidence of glaucoma and that ocular hypertension with normal visual fields and normal ONHs was not found in patients with AD, suggesting that the optic nerve seems to be less resistant to elevated IOP levels in AD patients[12]. Tamura et al. also found that the prevalence of open-angle glaucoma was significantly higher in AD patients than in controls[13]. Parisi reported a similar correlation between morphological and functional retinal impairment in patients with glaucoma and those with AD[14].

In addition, a decrease in amyloid-β (1-42) and an increase in tau were found in the vitreous fluid from patients with glaucoma, similar to the findings in the cerebrospinal fluid from patients with AD[15]. Others also reported the involvement of amyloid-β in animal models of glaucoma[16-19]. For example, in a rat model of chronic ocular hypertension, the RGCs demonstrated caspase activation and abnormal processing of amyloid precursor protein (APP), which includes production of amyloid-β[16]. Furthermore, APP and amyloid-β were increased in the RGC layer of DBA/2J glaucomatous mouse eyes[17]. APP and amyloid-β were also found to be highly expressed in the RGC layer of ocular hypertensive C57BL/6 mouse eyes[18]. Moreover, upregulation of amyloid-β was induced in the retina and ONH of a monkey model of chronic ocular hypertension[19].

Several reports implicate APOE in the pathogenesis of glaucoma, specifically NTG. A genetic study indicated

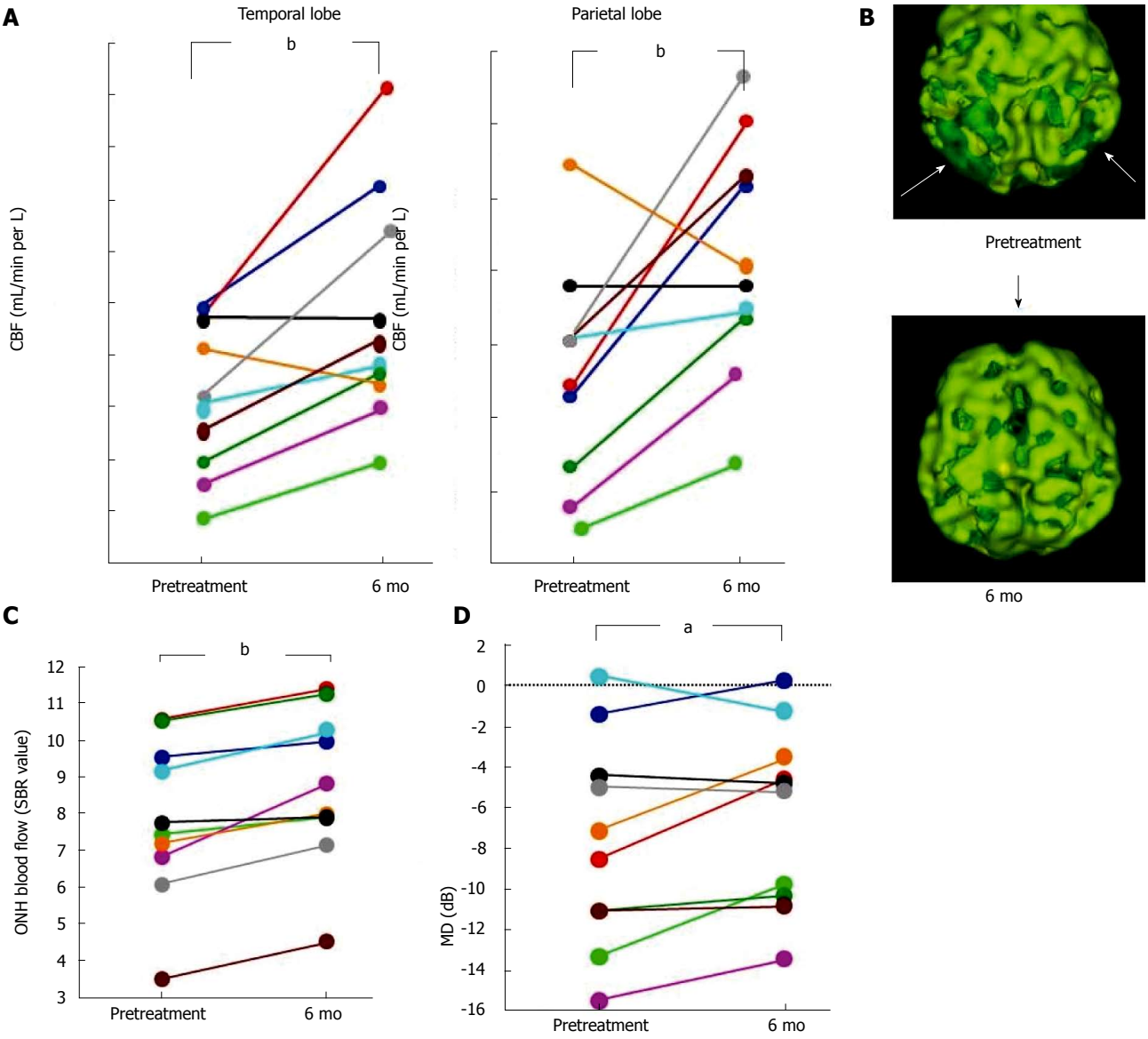

Figure 2 Changes in the cerebral blood flow of the temporal and parietal lobes (A), blood flow in the optic nerve head (C), and mean deviation (D) for each normal tension glaucoma patient after 6 mo of donepezil treatment, a representative change of SPECT images after 6 mo treatment (B). Arrows indicate obviously decreased CBF. ONH blood flow was evaluated by laser speckle flowgraphy, and the MD was obtained by the Humphrey visual field test (program 30-2). $^{a}P < 0.05$, $^{b}P < 0.01$ *vs* pretreatment, paired *t*-test. ONH: Optic nerve head; MD: Mean deviation; CBF: Cerebral blood flow.

that inheritance of the APOE ε4 allele is associated with elevated risks for glaucomatous changes that are not related to increased IOP[20]. Other genetic studies indicated that APOE-promoter single-nucleotide polymorphisms affect the phenotype of primary open-angle glaucoma and may be associated with a risk of glaucoma occurrence[21,22]. A recent report also revealed that patients with open-angle glaucoma had higher aqueous levels of multiple biomarkers of AD, including APOE, than did cataract patients[23].

CEREBRAL BLOOD FLOW (CBF) IN GLAUCOMA AND AD

Studies using single-photon emission computed tomography (SPECT) have indicated that CBF reductions were most common in the temporoparietal regions in AD patients[24]. Disturbed CBF has been reported not only in AD patients but also in glaucoma patients. Compared to controls, glaucoma patients were found to have a lower blood velocity in the middle cerebral artery (MCA) and an absence of vasoreactivity to hypoxia[25]. The MCA supplies blood to the anterior temporal lobes where blood flow is reduced in AD patients. In addition, the same group found a significant correlation between blood velocity in the MCA and central visual function measured by foveal cone electroretinograms and the visual field[26]. This finding suggests that diminished central visual function may be a manifestation of widespread cerebrovascular insufficiency in certain patients with glaucoma. Another group also reported enhanced transmission of oscillations in the mean arterial pressure onto CBF in patients with glaucoma including NTG[27]. They suggested that impaired cerebral autoregulation might contribute to an increased risk of cerebrovascular disorders in glau-

coma patients.

AD patients usually have a characteristic cerebral perfusion pattern, a decrease in CBF ranging from the parietal lobe to the temporal lobe, as shown in Figure 1B. In our SPECT study, we classified cerebral perfusion pattern into normal, AD-like (Figure 1A and C) and other patterns. We found that 22.6% of NTG patients exhibited an AD-like cerebral perfusion pattern[28]. Relative CBF in the parietal lobe was lower in NTG patients than in controls (Figure 1D)[28]. In a subsequent study, we increased the number of subjects and found that 36% of the NTG patients showed an AD-like pattern (Figure 1E)[29]. We also obtained a preliminary result regarding the effects of donepezil, an anti-AD drug, on NTG patients. Visual field, ONH blood flow, and CBF in the temporal and parietal lobes were improved after 6 mo of oral administration of donepezil although the IOP remained unchanged (Figure 2)[29]. This result implies that an AD-like cerebral perfusion abnormality might be involved in the pathogenesis of NTG in certain patients, and improving CBF can be a therapeutic strategy for glaucoma.

RECENT THERAPEUTICAL STRATEGIES FOR GLAUCOMA

Several types of recent or new therapeutic strategies for glaucoma have been suggested on the basis that similar pathological mechanisms underlie neuronal death in both AD and glaucoma. One such strategy is α-2 adrenergic receptor activation: compensating for common loss of noradrenergic innervation of RGCs and central neurons in glaucoma and AD[30]. A recent randomized, double-masked, multicenter clinical trial showed that NTG patients treated with an α-2 adrenergic receptor agonist brimonidine were less likely to show progression in visual field defects than were patients treated with timolol[31].

On the other hand, another report suggested that targeting different components of the formation and aggravation pathway for amyloid-β could be effective in reducing glaucomatous RGC apoptosis *in vivo*[32]. Several studies have reported the protective effects of an anti-AD drug donepezil (an acetylcholinesterase inhibitor) on RGC death *in vitro* and *in vivo*[33,34]. One of them suggested that not only the activation of acetylcholine receptors but also a mechanism unrelated to acetylcholinesterase inhibition might contribute to the protective effect of donepezil[34].

Recently, it was reported that administration of APOE-containing lipoproteins protected RGCs from glutamate-induced apoptosis *in vitro* and partially protected RGCs from neurodegeneration in glutamate aspartate transporter-deficient mice, which exhibit many features similar to human NTG[35].

In conclusion, eliciting the relevance of AD when considering the pathogenesis of glaucomatous optic neuropathy may provide novel therapeutic strategies for protecting the optic nerve in glaucoma.

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MINIREVIEWS

Endoscope-assisted vitrectomy

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Abstract

Ocular endoscopes enable ophthalmologists to observe any part of the retina without any limitations, including those caused by corneal opacities, the rim of the intraocular lens, cortical remnants, capsular opacities, a small pupil, and vitreous opacities. Moreover, ocular endoscopes enable the management of peripheral lesions without scleral indentation and are compatible with microincision vitrectomy surgery. The enlarged view under the endoscope, as obtained by drawing towards the lesion, appears to be another advantage. Rhegmatogenous retinal detachment with undetectable retinal breaks, trauma, endophthalmitis, scleral wounds with incarceration of the vitreous, and microcornea are indications for endoscopic vitrectomy. The combination of endoscopy and a wide-angle viewing system could compensate for the deficiencies of each technique and achieve more effective and safer surgical maneuvers. Endoscopy skills appear to be a great advantage for vitreoretinal surgeons; however, because endoscopies require a learning curve, becoming familiar with the handling of the endoscope through step-by-step learning is necessary.

Key words: Ocular endoscope; Vitrectomy; Retina; Microincision vitrectomy surgery; Retinal detachment

Core tip: Ocular endoscopes enable ophthalmologists to observe inside the eye and perform surgical procedures independent of the status of the cornea, pupil size and media. Moreover, endoscopes enable the management of peripheral lesions without scleral indentation. The enlarged view under the endoscope, as obtained by drawing towards the lesion, appears to be another advantage. Having endoscopy skills appears to be an advantage for ophthalmologists; however, because endoscopies require a learning curve, becoming familiar with the handling of the endoscope is necessary.

Kita M. Endoscope-assisted vitrectomy. *World J Ophthalmol* 2014; 4(3): 52-55 Available from: URL: http://www.wjgnet.com/2218-6239/full/v4/i3/52.htm DOI: http://dx.doi.org/10.5318/wjo.v4.i3.52

INTRODUCTION

Recently, endoscopic surgery has become popular in various fields of surgery. Overall, there has been a shift toward more non-invasive treatment, including in the field of vitreo-retinal surgery. In Japan, medical insurance has covered endoscopic vitrectomy since April 2012.

Many clinics are equipped with ocular endoscopes; however, many of these clinics lack skilled personnel to use the equipment. Performing endoscopic vitrectomy during surgery is difficult in many cases because of its learning curve. Becoming familiar with the handling of the endoscope is necessary in the clinical setting.

The advantages and indications of endoscope-assisted vitrectomy are presented here.

ADVANTAGES OF ENDOSCOPE-ASSISTED VITRECTOMY

Visualization independent of small pupil or cloudy media

Because the endoscope combines illumination with im-

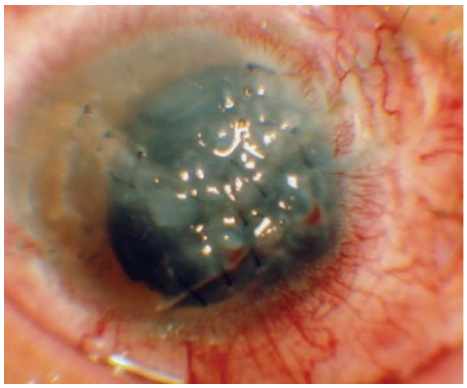

Figure 1 Anterior segment of the eye with severe penetrating corneal injury[6].

age fibers, ophthalmologists can see areas where the endoscope illuminates[1,2]. Therefore, the ocular endoscope enables ophthalmologists to observe any part of the retina and manipulate surgical procedures independent of corneal opacities, the rim of intraocular lens, cortical remnants, capsular opacities, a small pupil, and vitreous opacities[3,4] (Figure 1).

Observation and manipulation of the retinal periphery without scleral depression

Recently, a wide-angle viewing system has become popular, as it can easily provide a panoramic view of the surgical field. However, even in this system, an indentation of the sclera is inevitable when observing or manipulating the periphery, which could cause intraoperative pain and postoperative inflammatory reactions, such as fibrinous exudates.

The endoscope enables ophthalmologists to observe the peripheral area of the fundus and the anterior part of the eye without scleral indentation (Figure 2A), which could contribute to a less invasive surgery and faster postoperative visual rehabilitation[1-4].

Moreover, when the perfluorocarbon liquid (PFCL) fills to the posterior surface of the iris, a stream of the infusion could cause the formation of PFCL droplets that appear as "fish-eggs". Even if the PFCL is gently injected into the shape of a ball under the valved trocar system, scleral indentation might still cause the PFCL fish-eggs. Endoscopic maneuvers in the peripheral areas without scleral indentation can prevent the formation of PFCL fish-eggs.

Magnified view

A wide-angle viewing system is unsuitable for the observation or detection of subtle changes in the fundus because the image in the system is small. On the other hand, because endoscopes can magnify the view by closing in on the retina, the images obtained are clearer and larger than those obtained with a wide-angle viewing system or a microscope. Therefore, endoscopes can facilitate the detection and management of tiny lesions[5] (Figure 2B).

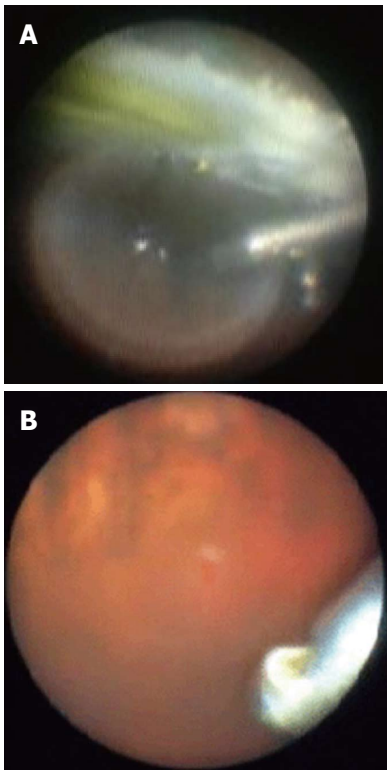

Figure 2 Intraoperative endoscopic view. A: A bubble of silicone oil and yellow IOL can be observed; B: A tiny retinal tear was identified[5].

Reconfirmation of the periphery

At the end of a surgical case, a 360-degree inspection of the periphery under the endoscope ensures that the vitrectomy was completed without any complications, such as iatrogenic retinal breaks, consequently reducing the risk of re-operations[3,4].

INDICATIONS FOR ENDOSCOPE-ASSISTED VITRECTOMY

Rhegmatogenous retinal detachment with preoperatively undetected retinal breaks

In rhegmatogenous retinal detachment, one of the poor prognostic factors for surgical success is the inability to detect retinal breaks preoperatively. Undiagnosed retinal breaks, which are typically characterized as tiny breaks located near the ora serrata, appear to be the main cause for the lower success rate of initial surgery in pseudophakic and aphakic retinal detachment compared to phakic cases. Furthermore, capsular opacity, lens remnants, and/or a small pupil could prevent the identification of these retinal breaks. Therefore, the visualization of retinal breaks can simplify surgery and improve the reattachment rate.

There are several advantages for using the endoscope[5]. Endoscopes are suitable for the observation of the periphery, independent of small pupil and media opacity, without causing scleral depression, and help detect tiny lesions in the retina by enlarging the images (Fig-

ure 2B). Dynamic scleral depressions sometimes make tiny retinal breaks unclear to close the retinal flaps.

The endoscopic identification of retinal breaks enables ophthalmologists to perform retinopexy only around the breaks. In contrast, when using a standard 360-degree peripheral laser or cryoretinopexy for vitrectomy, retinal breaks remain unidentified. Excessive retinopexy may cause intraoperative pain and complications, such as vitreous hemorrhage or iatrogenic breaks, postoperative inflammation and proliferative change.

Trauma

In severe penetrating corneal injuries, using a temporary keratoprosthesis during vitrectomy followed by keratoplasty is thought to be beneficial because of the difficulty of observation through the cornea. However, complications may arise, including suprachoroidal hemorrhage and graft failure.

With a floating contact on the cornea or a wide-angle viewing system, endoscopes can overcome poor corneal conditions, which impair observations into the eye (Figure 1). Furthermore, the endoscope allows ophthalmologists to observe the peripheral part of the retina, vitreous base, pars plana, and pars plicata without manipulating the anterior chamber and causing scleral depression, which could cause fluid leakage or hemorrhage from the penetrating wounds in open eye injuries[6].

The enlarged, clear image with an endoscope can facilitate the detection of retinal breaks not preoperatively identified.

Endophthalmitis

In inflammation, observations *via* the pupil are sometimes difficult due to the poor media conditions, such as corneal opacity, keratoprecipitate, posterior synechiae of the iris, small pupil, and cell adherence to IOL (intraocular lens). Managing vitrectomies via the pupil when severe inflammatory cells invade the cornea is impossible because of the dense corneal opacity. These cases are an absolute indication of endoscopic use[3,4].

Endoscopic vitrectomy without any manipulation of the anterior chamber and scleral depression could reduce the risks of intraoperative perforations of the eye wall and severe postoperative inflammation.

Scleral wounds with incarceration of the vitreous

When retinal breaks are generated due to the incarceration of the vitreous or/and retina into the scleral wound or trocar, depressing the sclera to observe the lesion through a microscope is dangerous because of the risk of enlarging the retinal break.

In these situations, releasing the incarceration under the endoscope, without indenting the sclera, appears to be inevitably safer[3,4].

Microcornea

Microcornea is a rare congenital eye malformation. In most reports of microcornea, microphthalmia has also been observed. However, microcornea can also be associated with normal size globes or even macrophthalmia. In these cases, especially with a small pupil, the morphological features prevent the observation of the peripheral retina, even with a scleral depression and/or wide-angle viewing system.

Endoscope-assisted vitrectomy is advantageous for the management of these lesions, such as retinal detachments[7].

EFFICACY IN MIVS

Recently, microincision vitrectomy surgery (MIVS) has become popular and 20G, 23G, and 25G endoscope fibers for small-gage surgery are commercially available in Japan.

The size of the field of view depends on the focusing lens attached to the fiber; therefore, there is no difference in the size of view between the 20G and small-gage systems. However, the size of the image depends on the pixels of the fiber; therefore, a smaller gage system tends to have a smaller image. However, the size of the image can be enlarged with a special instrument called the iS Board (Fiber Tec, Tokyo, Japan), which can modify the size, contrast, brightness and color tone of the image in real-time. The iS Board allows ophthalmologists to more easily perform endoscopic vitrectomies in MIVS[1-4].

In MIVS, scleral depression is sometimes difficult because of the transconjunctival approach. Furthermore, compared with 20G vitrectomy, a longer period of time is required to restore the intra-ocular pressure after releasing the scleral depression because less fluid is supplied from the smaller gage infusion. Therefore, endoscopic vitrectomy is advantageous for the peripheral management in MIVS where scleral indentation is likely[3,4].

USING ENDOSCOPE WITH A WIDE-ANGLE VIEWING SYSTEM

The wide-angle viewing system enables ophthalmologists to instantaneously observe a panoramic fundus; however, the image is small. In contrast, endoscopes enable ophthalmologists to enlarge the image by closing in on the retina. However, this field of observation is narrow, and the view is non-stereoscopic. It is more efficient to choose the best tool of visualization at each step of the surgery. For example, in retinal detachment cases, core vitrectomy, creating PVD and F/A exchange should be visualized with a wide- angle view, contact lens are suitable for membrane peeling, and endoscopes are suitable for peripheral maneuvers.

Combining the maneuvers of an endoscope and a wide-angle viewing system, called "hybrid vitrectomy", could compensate for the deficits of each system and allow a more effective and safer surgical management[3,4].

SURGICAL TIPS

Because some training is required to obtain endoscopy

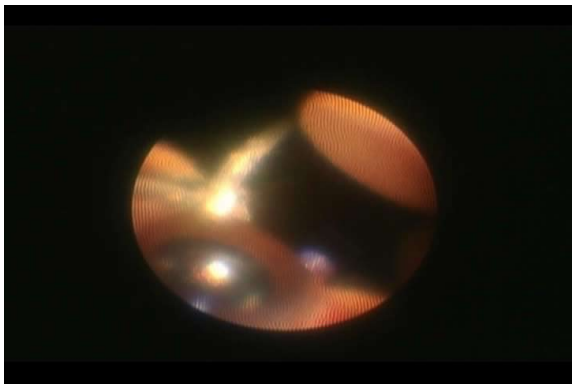

Figure 3 The direction should be arranged properly by projecting the fingers of the right hand outside of the eye.

skills, a step-by-step process is recommended to shorten the learning curve[8-10]. First, the endoscope should be used in the left hand to illuminate. Next, observations of the peripheral fundus should be attempted while the right hand stays out of the eye. The endoscope probe should be more horizontal than would be expected to observe the ora serrata. Endoscopic observation should be attempted while the vitrectomy cutter in the right hand is inside the eye. Subsequently, cutting the vitreous hemorrhage or applying laser photocoagulation under the endoscope should be attempted. Until an ophthalmologist feels comfortable using the endoscope, endoscopes are more suitable for use in usual cases, where the endoscopes are not necessary to perform vitrectomies. Beginning to use an endoscope in cases where the endoscope is necessary is difficult. Ophthalmologists should become familiar with manipulating the endoscope by frequently using it.

Orientation is the most important point when using the endoscope. First, the direction should be properly arranged by projecting the fingers of the right hand outside of the eye (Figure 3). Then, the endoscopic probe is inserted into the eye, followed by the re-arrangement of the direction by projecting the vitrectomy cutter at the 4:00 position on the screen[8-10].

To observe the peripheral area at approximately 2:00, the endoscope probe should be held with the right hand instead of the usual left hand and inserted from the port at approximately 10:00. A 360-degree periphery can be observed under the endoscope by the manipulation with both hands.

The monitor for the endoscopic view is another key point, and it should be located at a comfortable position for the surgeon to turn from the microscope to its monitor.

The maintenance of the fiber is also important for the proper visualization of the fundus through the endoscope during surgery.

FUTURE DEVELOPMENT

In Japan, not only disposable fibers but also re-usable fibers for MIVS have been available recently. According to the smaller-gage vitrectomy system, such as 27G or 29G, smaller endoscope fibers could be developed in the near future. A multifunctional endoscope with an attachment laser or angiographic filter might be useful. A system that can provide 3-dimensional images might make manipulations easier during surgeries.

CONCLUSION

In endoscopy, ophthalmologists have a narrow field of mono-vision. Because microscopes have a wider stereovision, they are advantageous in most situations in vitrectomy. Therefore, it is unnecessary to use endoscopic maneuvers from the beginning to end of the surgery. Choosing the best tool for visualization at each step of the surgery is important.

The efficacy of the endoscope in vitrectomy surgery is clear; therefore, obtaining understanding of and competency with the endoscope is an advantage.

Increasing the frequency and proper use of the endoscope by more surgeons can ensure the improvement of the endoscope as a more convenient tool in vitrectomy surgeries.

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MINIREVIEWS

Updates in uveitic macular edema

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Abstract

Macular edema is one of the most common vision-threatening complications of uveitis noted in one third of patients with uveitis. The release of a number of inflammatory mediators induces retinal vascular hyper-permeability leading to uveitic macular edema (UME) which most commonly is of cystoid shape. Fluorescein angiography and non-invasive spectral-domain optical coherence tomography are standard procedures for diagnosis and follow-up of UME with some innovations such as scanning laser ophthalmoscope retro-mode imaging. Effective management of UME requires thorough understanding of the individual case. Proper control of intraocular inflammation is mandatory before targeting macular edema itself. Mainstay of treatment is immunosuppressive therapy with various drug delivery routes including topical, local subconjunctival, peribulbar and sub-Tenon's, intravitreal and systemic. Clinical trials with biologics are under way to study the efficacy of these agents in suppressing intraocular inflammation and resolution of UME. Visual prognosis in UME depends on numerous factors. Younger age and better visual acuity at baseline are associated with more favorable visual outcome in most studies

Key words: Intraocular inflammation; Uveitic macular edema; Fluorescein angiography; Optical coherence tomography; Corticosteroid therapy; Drug delivery; Clinical trials

Core tip: Cystoid macular edema is among leading causes of visual loss in patients with uveitis. Inflammatory cytokines such as interferon-gamma, interleukin-2, interleukin-10, tumor necrosis factor-alpha and prostaglandins are powerful inflammatory mediators which along with the vascular endothelial growth factor are potent mediators of increased vascular permeability in uveitic macular edema. Scanning laser ophthalmoscope in retro-mode is a novel imaging modality that can show each cystoid space located in any layer of the retina and allows the detection of the extent of cystoid macular edema.

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INTRODUCTION

Macular edema is one of the most common vision-threatening complications of uveitis. It can affect patients with different types of ocular inflammation[1,2]. Cystoid macular edema (CME), the most common structural type of uveitic macular edema, was found to be the most important cause of both blindness and visual impairment among patients with uveitis, it was noted in 33% of all uveitis patients[3,4]. Visual loss due to cystoid macular edema in patients with uveitis, occurs predominantly in older patients with chronic uveitis[5]. Chronic macular edema has a significant influence on the quality of life of the patients, this is especially important as it tends to affect young people, often between 30 and 50 years of age[6,7].

In adults, cystoid macular edema is the leading cause

of visual loss in patients with uveitis. However, the incidence of inflammatory CME in children seems to be lower and it is still the third leading cause of visual loss after macular scars and secondary glaucoma[8]. Macular edema in patients with uveitis was found to account for 41% of visual impairment and 29% of blindness[9]. In this short review we summarize current updates on pathophysiology, diagnosis and treatment of uveitic macular edema.

PATHOPHYSIOLOGY

Effective management of uveitic macular edema requires thorough understanding of the underlying mechanisms of its formation. However, the pathogenesis of uveitic macular edema is not completely understood. Under normal conditions, the fluid volume and content of the macula is controlled by the blood retinal barriers and the pump function of the retinal pigment epithelial cells. The blood retinal barriers are composed of the inner retinal barrier formed by tight junctions of the endothelial cells lining the retinal capillaries and the outer retinal barrier formed by tight junctions between retinal pigment epithelial cells[8]. Most commonly, macular edema results from abnormal hyperpermeability of retinal blood vessels. Among the various tight junction molecules in blood vessel wall, downregulation of occludin has been reported most consistently in the context of blood-retina barrier (BRB) breakdown as well as modulation of aquaporins and dysregulation of caveolar transport[10]. This increase in vascular permeability leads to extravasation of fluid, proteins and other macromolecules into the retinal interstitium[11]. The release of a number of inflammatory mediators induces retinal vascular hyperpermeability. These inflammatory cytokines include interferon-gamma, interleukin-2, interleukin-10 and tumor necrosis factor-alpha[2]. Prostaglandins are powerful lipid derived inflammatory mediators which are generated from the phospholipids in the cell membrane[12,13].

Vascular endothelial growth factor (VEGF) was found to be a potent mediator of increased vascular permeability[14]. Interestingly, it was noted that patients with uveitis and CME have higher concentrations of vascular endothelial growth factor in the aqueous humor as compared with those without CME[15]. Another important factor that contributes to increased vascular leakage is the endothelial damage induced by adherence of leukocyte to the vessel walls, a phenomenon termed leukostasis which is mediated by nitric oxide, adhesion molecules, and other inflammatory mediators[16,17]. The dysfunction of the BRB may not explain the mechanism of macular edema in all cases. Other possible factors that may contribute to the occurrence of maculopathy include the presence of active inflammation, macular or choroidal ischaemia (as a result of active vasculitis), and vitreoretinal traction. Accordingly, treatment of persistent uveitic macular edema will be more successful if the underlying pathogenic mechanisms are properly addressed[18].

The release and diffusion of cytokines may have the predominant role in case of acute inflammation, but the exact factors and events responsible for the development of chronic macular edema in the setting of controlled inflammation have not yet been clearly identified[5]. However, persistence of CME might be secondary to previous inflammatory insults to the retinal pigment epithelium, blood-retina barrier, and persistent cytokines[19]. Leakage from the optic nerve, which is often present in uveitis, may also contribute to the development of persistent macular edema[20,21].

Leakage was found to be amplified by factors that affect the integrity of the retinal blood vessels such as vasodilatation, increased intraluminal pressure, and increased blood flow. Hence, patients with concurrent cardiovascular disease, hypertension, diabetes, or hyperlipidemia have an increased risk of developing macular edema and when present it tends to be more persistent[22]. Smoking was noted to be a risk factor for cystoid macular edema in cases with intermediate uveitis[23,24]. Recently, it was found that two functional genetic variants of interferon regulatory factor 5 (*IRF5*) may play a role in the development of macular edema in non-anterior uveitis patients through regulation of induction of type I interferon[25].

DIAGNOSIS

The presence of macular edema can be detected clinically in cases with clear media. However, biomicroscopic evaluation of macular edema may be difficult when the amount of the fluid and the anatomical changes are minimal. In addition, it is required to have ways to document the extent of the macular edema in order to monitor the progression of macular edema following different treatment modalities.

Fluorescein angiography is a conventional method for the assessment of UME. It is particularly valuable to assess the retinal vascular integrity and to characterize the area of the foveal avascular zone. Fluorescein angiography can also show leakage around optic nerve head which is a common finding in cases with uveitis[26]. The drawbacks of fluorescein angiography include the invasive nature and the need of the contrast with its potential side effects. Furthermore, the interpretation of the fluorescein angiograms might not be easy in the presence of extensive areas of hemorrhage or exudates[27].

Optical coherence tomography is an effective diagnostic modality for detection of macular edema which produces B-scan cross sectional images of the retinal layers that are comparable to histopathology specimens. It not only allows the determination of the distribution of fluid within the retinal layers but also allows quantification of retinal thickness particularly in patients with CME[28,29]. Three patterns of macular edema were noted in patients with uveitis studied by optical coherence tomography: diffuse macular edema, cystoid macular edema, and serous retinal detachment[29]. In a recent report from the Multicenter Uveitis Steroid Treatment trial,

macular edema was associated with impaired visual acuity. Different phenotypes of macular edema were associated with different degrees of visual impairment: cystoid changes without retinal thickening were associated with moderately impaired visual acuity (-5 ETDRS letters), but visual acuity was worse in eyes with retinal thickening (-13 letters) and with both cysts and thickening (-19 letters). Uveitis was also associated with impaired visual field sensitivity, but eyes with macular edema had even worse visual field sensitivity[30].

Epiretinal membrane coexists in a significant percentage of patients with uveitis and may be associated with persistence of macular edema. OCT is helpful in detection and characterization of uveitic ERM[29].

Several studies evaluated the agreement between fluorescein angiography and optical coherence tomography results for the diagnosis of macular edema in patients with uveitis. Optical coherence tomography and fluorescein angiography were found to offer only moderate agreement regarding macular edema status in patients with uveitis, probably because each imaging modality might demonstrate related but nonidentical macular pathologic features. In four hundred seventy-nine eyes with uveitis from 255 patients, macular leakage was present in 40% of cases free of macular thickness with OCT, whereas macular thickness was present in 34% of cases without macular leakage[31]. Because of its lower cost, greater safety, and greater likelihood of obtaining usable information, OCT may be the best initial and follow-up test for evaluation of suspected macular edema. However, obtaining the second test after negative results of the first seems justified when detection of macular leakage or macular thickness would alter management[31]. Both FA and high-resolution OCT are highly sensitive techniques and correlate well in detection of ME. However, there is a small chance that when each test performed alone it might miss existing subtle ME[32]. Therefore, FA and OCT are complementary investigations, each revealing different aspects of the pathophysiology of uveitic ME[33].

The retro-mode of the scanning laser ophthalmoscope is a new method of detecting abnormalities in the retina. It uses an infrared laser and an aperture with a modified central stop that is displaced laterally from the confocal light path. This optical arrangement allows for a clearer and pseudo-3-dimensional image[34]. Scanning laser ophthalmoscope in the retro-mode can show each cystoid space located in any layer of the retina and allows the detection of the extent of cystoid macular oedema[35,36].

TREATMENT

Chronic macular edema may lead to permanent loss of vision if not properly treated. It is associated with damage to photoreceptors by ischemia and might lead to retinal thinning and fibrosis[2]. There are no guidelines or consensus on when and how to treat uveitic macular edema and the evidence strength for treatment of macular edema in uveitis is overall low[37]. Macular edema associated with active inflammation requires immediate intervention. Several treatment options exist to address macular edema. The approach used depends on several factors including the laterality of disease, the response to therapy and the side effects of the proposed medication. Management should start with an attempt to treat the underlying cause and control of the ocular inflammation.

Topical therapy for treatment of uveitic macular edema includes corticosteroid and non-steroidal anti-inflammatory drugs (NSAIDs). Treatment with steroids and NSAIDs has been shown to inhibit the release of the inflammatory mediators and was found to decrease vascular permeability[38]. There was no significant difference in the results of treatment in the studies comparing topical NSAIDs with corticosteroids[38].

In the absence of vitreoretinal traction, the administration of indomethacin 0.5% eye drops four times per day in eyes affected with uveitic ME from different etiologies, compared with placebo, was associated with a significant reduction in ME at the 6-mo follow-up visit, as measured by spectral-domain optical coherence tomography[39].

In addition to topical drops and systemic medications, there are various drug delivery routes to treat UME. Local treatment includes injections given subconjuctivally or in the sub-Tenon space, intravitreal injections of drugs and intraocular implantation devices. The advantage of all these is effective delivery of the drug to the proximity of target tissue. Resistant cases of uveitic CME require higher macular concentrations of corticosteroid agents; this can be usually achieved with local therapy such as posterior sub-Tenon injection[10]. Intravitreal triamcinolone acetonide allows high steroid concentration to act locally for maximal effect and duration (Figures 1 and 2). Although intravitreal triamcinolone was found to be often effective in reducing CME, it may not always be effective in improving visual acuity, likely because of pre-existing or long-standing macular damage[40].

Intraocular steroid sustained-delivery device implantation is a relatively new treatment approach for patients requiring frequent intravitreal triamcinolone acetonide injections or chronic treatment with systemic corticosteroids and/or immunosuppressive agents. The Retisert (fluocinolone acetone; Bausch and Lomb Place, Rochester, NY, United States) implant is a non-biodegradable implant, whereas the Ozurdex (dexamethasone; Allergan, Irvine, CA, United States) is biodegradable implant[41,42]. The accumulated effect of repeat dexamethasone pellet implantations was found to improve retinal thickness and resolve ocular inflammation, resulting in restoration of ocular function[43]. Potential complications of all forms of local steroid delivery include increased intraocular pressure and cataract progression[44-46].

Intravitreal injections of anti-VEFG were shown to be useful and therapeutically beneficial in refractory uveitic CME. Intravitreal bevacizumab was found to be as-

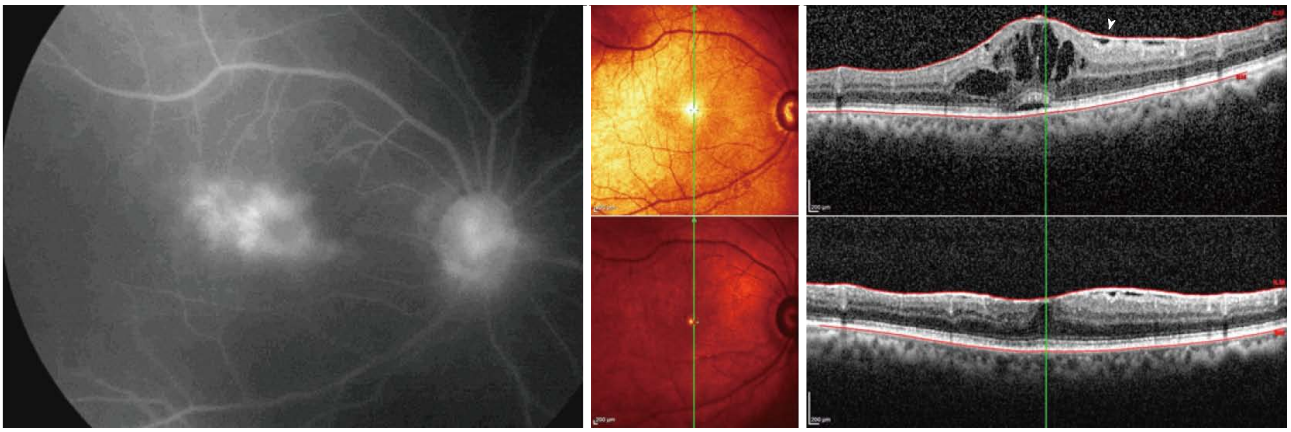

Figure 1 Uveitic macular edema. Left: Late frame of fluorescein angiogram showing dye leakage to the macular area with cystoid pattern (cystoid macular edema) due to uveitis. Upper right: Spectral-domain optical coherence tomography orientation and B-scans of the same eye showing cystoid macular edema with small amount of subfoveal fluid and associated epiretinal membrane (white arrowhead). Lower right: Spectral-domain optical coherence tomography orientation and B-scans of the same eye 3 mo after intravitreal triamcinolone acetonide intravitreal injection demonstrates complete resolution of intraretinal and subfoveal fluid with persistence of epiretinal membrane. Visual acuity improved from 20/100 to 20/30.

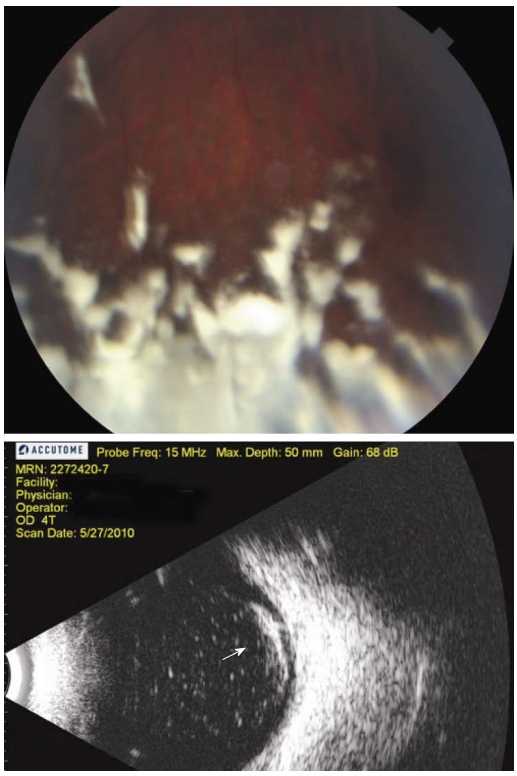

Figure 2 Intravitreal steroid treatment. Upper panel: Fundus photograph showing crystals of triamcinolone acetonide injected intravitreally; Lower panel: Ultrasound B-scan of the same eye showing crystals of triamcinolone acetonide injected intravitreally (white arrow).

sociated with anatomic and visual improvement in uveitis patients with CME resistant to medical therapy that persists despite control of the uveitis[19]. Ranibizumab is an antibody fragment which neutralizes all VEGF isoforms and bioactive fragments which also demonstrated a significant improvement in visual acuity and a reduction in macular edema[47,48]. Intravitreal adalimumab was shown in some studies to be of help for refractory uveitis-related macular edema[49]. Local injection therapy can be associated with rare complications. Endophthalmitis and rhegmatogenous retinal detachments have been reported with intravitreal injections of anti-VEFG performed[50,51].

Intravitreal NSAIDs were also evaluated in patients with refractory uveitic cystoid macular edema. Intravitreal injection of diclofenac insignificantly reduced central macular thickness but this was not associated with visual improvement[52].

Several systemic treatment options exist for treating uveitic macular edema including systemic corticosteroids, systemic NSAIDs, systemic immunomodulators, biologic agents and RPE pump inhibitors. Oral steroids are usually reserved to treat patients with significant vision-threatening uveitis as they are associated with systemic side effects[53]. On the other hand, systemic NSAIDs were found to have a limited role, if any, in the treatment of inflammatory cystoid macular edema[54]. Systemic immunomodulator drugs have been found to be effective in the management of uveitic macular edema. Treatment with mycophenolate mofetil may lead to resolution of CME and improve the mean BCVA in patients with uveitis[55,56].

Several biologic agents were evaluated for UME. Intravenous infliximab was found to improve visual acuity and decrease macular thickness in patients with chronic cystoid macular edema associated with uveitis[57]. Efalizumab is an intercellular adhesion molecule inhibitor that was reported as a potential therapy to improve visual acuity and reduce macuar thickness for refractory uveitic macular edema[58]. Acetazolamide, an RPE pump stimulator, may be useful for chronic CME in uveitis. However, the effect is better in cases with quiescent uveitis than in those with chronically active disease[59]. Intravitreal adalimumab showed no efficacy in improving best-corrected visual acuity or reducing central retinal thickness in patients with chronic uveitic macular edema[49].

Pars plana vitrectomy may have a role in the man-

agement of selected cases with uveitic macular edema. Clearing vitreous cavity decreases burden of circularing inflammatory cytokines which may contribute to persistence of UME. In eyes with vitreous adhesions and macular traction, vitrectomy surgery with removal of all vitreous adhesions may results in good anatomic and visual outcomes. In a prospective, interventional, randomized, controlled study of 23 eyes of 23 patients, the mean visual acuity in the surgical group improved significantly from logMAR 1.0 (± 0.62) at baseline to 0.55 (± 0.29) at 6 mo (P = 0.011), with 5 (42%) eyes reaching vision of 20/40 or better. CME after vitrectomy improved in the fluorescein angiogram in 4 (33%) eyes, remained unchanged in 7 (58%) eyes and deteriorated in 1 (8%) eye[60]. In addition, vitrectomy has an influence on the efficacy of triamcinolone acetonide injectable solution. In a retrospective review of 20 eyes, it was found that, after intravitreal triamcinolone injection for chronic CME, the mean visual acuity at last follow-up showed statistically significant improvement in non-vitrectomized eyes compared to the almost unaltered mean visual acuity for vitrectomized eyes[61]. A recent study with limited follow-up has shown that treatment with dexamethasone intravitreal implant injection for uveitic macular edema in vitrectomized eyes was associated with favorable visual outcomes and had an acceptable safety profile[62].

Visual prognosis in UME depends on numerous factors. A study reported longitudinal outcomes after 48 mo median follow-up period. Visual acuity at the final follow-up improved in 69%, was deteriorated in 19%, and remained unchanged in 12% of eyes. Younger age and better visual acuity at baseline were associated with more favorable visual outcome. Optical coherence tomography documentation of improvement or total resolution of UCME was observed in 77% at the final follow-up[63].

In conclusion, effective management of uveitic macular edema requires thorough understanding of the underlying mechanisms. Proper control of intraocular inflammation is mandatory before targeting macular edema itself. Various diagnostic and therapeutic approaches exist for treatment and monitoring of uveitic macular edema.

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MINIREVIEWS

Orthokeratology lens related infections

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Abstract

Orthokeratology is a reversible technique that temporarily changes the curvature of the cornea with the aim of addressing refractive errors. The United States Food and Drug Administration (FDA) granted approval for using reverse geometry contact lenses to correct myopia without any age restriction. Information from the pre-market applications to the FDA was rated as level Ⅱ evidence. Another unapproved use of overnight orthokeratology is for the prevention of myopic progression. Although orthokeratology is advocated to reduce myopic progression, there are limited long-term studies with substantial evidence of its benefits. Much of this evidence comes from non-robust experimental studies using historical or self-selected controls with relative high dropout rates. Although some positive results have been published in temporarily reducing the myopic refractive error and its progression, the use of these lenses can be associated with serious complications such as microbial keratitis. Microbial keratitis is a potentially vision-threatening adverse response associated with contact lens wear. In fact, contact lens wear has been shown to be the predominant risk factor of microbial keratitis in some developed countries. Most of the published cases on overnight orthokeratology related microbial keratitis occurred in children or adolescents. Parents considering orthokeratology must make an informed decision about its temporary benefit and its potential for permanent loss of vision. The ophthalmic community should be reminded of the potential complications of orthokeratology.

Key words: Orthokeratology; Infections; Microbial keratitis; Cornea; Corneal ulcer; Contact lens; Myopia

Core tip: Orthokeratology uses specially designed rigid contact lenses to temporarily reshape the cornea to ameliorate refractive errors and it has also been suggested to slow the progression of myopia. None of the published studies to date in assessing its efficacy are rated as level Ⅰ evidence. Orthokeratology carries the risk of microbial keratitis, which is potentially sight threatening and the safety of orthokeratology remains difficult to assess. Practitioners prescribing orthokeratology must receive appropriate training with respect to the local standards, inform patients and/or their parents of the potential risks, and ensure their patients' compliance in proper handling of the day to day care of their lenses to minimize the infective risks.

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INTRODUCTION

Orthokeratology is defined as the reduction, modification, or elimination of refractive anomalies by the pro-

grammed application of contact lenses[1]. Modern day orthokeratology was first advocated during the Second World Contact Lens Congress in Chicago in 1962, where George Jessen, the father of orthokeratology, introduced fitted polymethyl methacrylate (PMMA) contact lenses which had a curve flatter than the cornea to alter the curvature of the cornea and reduce myopia[1]. These lenses were worn during daytime and provided clear uncorrected vision for a few hours after they were removed in the afternoon. Over the next few decades, few other studies comparing daily wear of orthokeratology lenses reported similar modest but not significantly different myopic reduction as compared with conventional alignment fitted lens. Disappointment began to set in as inducible corneal astigmatism was reported due to lens instability. Variable and temporary refractive outcomes were observed, requiring continuous use of retainer lens to maintain its refractive effectiveness and/stabilisation.

Re-emergence of interest in this technique came in the late 1980's with the development of rigid gas permeable (RGP) lens that has a significantly higher oxygen transmission (Dk). Such material allows for a relatively safer closed-eye contact lens usage[2]. This led to the concept of overnight orthokeratology (OOK) where lenses are worn during the night time and removed during the daytime, allowing unaided vision during waking hours. Computer-assisted corneal topographic mapping also provided more detailed assessment of the elevation and curvature of the cornea, allowing more accurate lens design and fitting. Conventional rigid lens surfaces are designed to have a central base surrounded with progressively flattening concentric curves. With the development of reverse geometry lenses, designed to have a flat-back central optical zone with steeper intermediate zone, more accelerated flattening of the central corneal zone is possible compared to the previous lens designs[3].

This review will highlight the published literature on the efficacy of orthokeratology and the evidence of potential limitations, and outline the complications related to the use of these lenses.

PRINCIPLE AND EVIDENCE OF EFFICACY

Orthokeratology temporarily reduces the overall refractive power by flattening the central cornea to reduce the corneal sagittal height in order to reduce myopia[4]. The corneal periphery becomes relatively thicker, enhancing the peripheral corneal curvature. There is conflicting evidence about the time sequences of these events, but the combined effect is proposed to be the mechanism behind the refractive changes[5]. Thinning of central epithelium has been observed with optical coherence tomography[6]. Correlating with the morphological changes, unaided vision usually improves on an average by 1 wk, and stabilizes by 1 mo[7]. However, such visual improvement is transient, unless retainer lenses are continuously used at night time to maintain the flattened central cornea, where the frequency of use would depend on the degree of myopia, and ranges from every 1-2 nights to maintain the flattening effect[7]. The US Food and Drug Administration (FDA) approved the Paragon Corneal Refractive Therapy (CRT) for myopia reduction in 2002 based on their premarket study consisting of 205 subjects, only 24 of whom were between the age of 12 and 18 years[8]. During the evaluation, the FDA advisory panel commented that they would only recommend the approval of Paragon CRT be limited to patients 18 years and older, but FDA granted the approval of OOK without any age restriction. Later in 2004, Euclid Systems also received FDA approval for their orthokeratology to control myopia.

An unapproved use of OOK is for prevention of myopic progression. It is proposed that OOK prevents myopia progression *via* "peripheral hyperopic defocus"[9]. This theory suggests that the peripherally flatter cornea reduces peripheral hyperopia by aligning the image shell onto the mid peripheral retina, signalling the peripheral retina to control axial elongation. This controversial theory was tested in studies and it was found that relative peripheral hyperopia exerts little consistent influence on the rate of myopia progression or axial elongation[10]. The reported reduction in axial length also may be attributed to the gradual slowing of myopic progression in the control group with age, which may be expected. The published studies so far were neither randomized nor prospective, leading to observer bias. Five studies using historical or self-selected controls reported relative slower myopic progression (by 32%-55%) in low-to-moderately myopic children wearing OK lenses compared with those wearing conventional eyeglasses[11-14] or single-vision soft contact lenses[15]. The dropout rate reported in these studies with orthokeratology varies from 6%[14] to 30%[15]. The Longitudinal Orthokeratology Research in Children trial studied 35 children in Hong Kong who wore OK lenses for 2 years[11]. The authors found that the axial length in the orthokeratology group increased by 0.29 mm *vs* 0.54 mm for the control group. However, a major drawback in this study was that a historical control group of children wearing single vision lenses was used as the control. The Corneal Reshaping and Yearly Observation of Nearsightedness Pilot Study[15] compared 28 participants using corneal reshaping contact lenses to a historical control subject who were randomly assigned to wear soft contact lenses during the Contact Lens and Myopia Progression study[16]. Although the authors reported the annual rate of change in axial length was 0.16 mm per year less for corneal reshaping lens wearers than soft contact lens wearers ($P = 0.00004$), the low number of participants, the choice of control, as well as a 30% dropout rate limit the strength of the conclusions drawn from this study. Another study followed the OOK participants over 5 years and reported that changes in axial length over each year were significantly different; however, by the end of year 5, the changes in axial length were no longer significantly different ($P = 0.8633$)[13]. A recently published randomized controlled trial attempted to determine whether OK was effective in

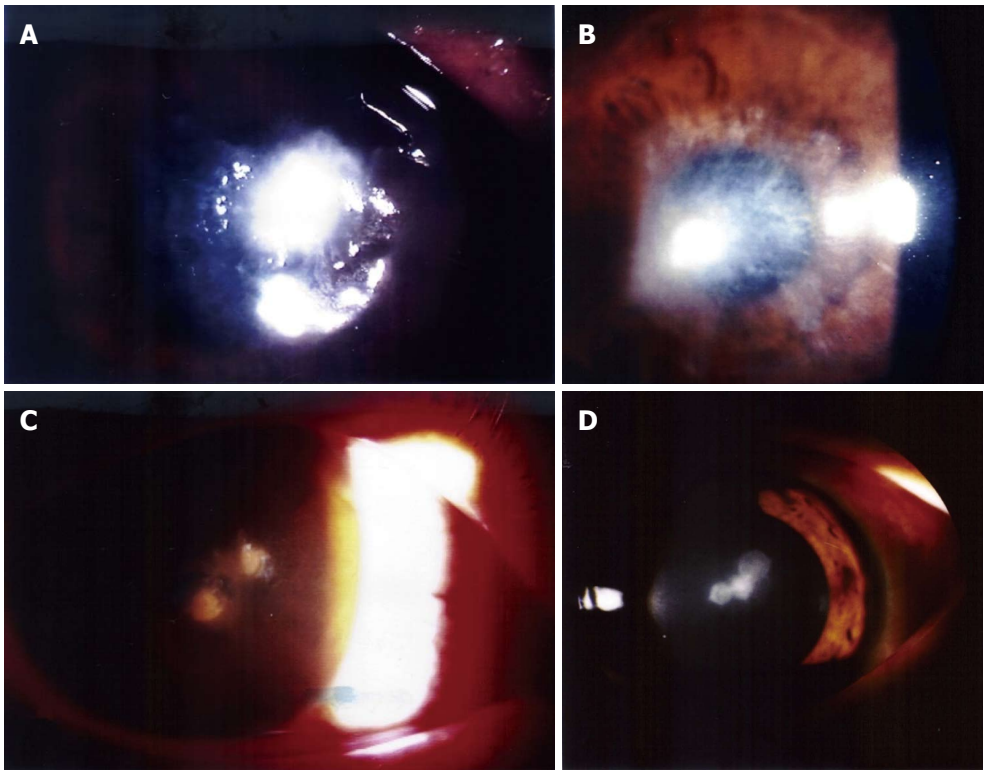

Figure 1 Microbial keratitis raises significant concerns in using overnight orthokeratology lenses. A: Presentation of a 13-year old girl who wore OKL for 36 mo with nocturnal wear at 10 h. Culture grew Pseudomonas aeruginosa; B: The 13-year-old girl with scar after treatment. Best corrected vision was 20/200 (plano/-5.00 × 165°); C: Presentation of a 12-year-old boy who wore OKL for 7 mo with nocturnal wear at 10 h. Culture grew Pseudomonas aeruginosa; D: The 12-year-old boy with scar after treatment.

slowing myopia progression[17]. They found that subjects wearing OOK lenses had a slower axial elongation by 43% compared with those wearing single-vision glasses. Younger children less than 7 years of age had faster axial elongation and may have additional benefit from early OK treatment. However, the examiners measuring the axial length were not masked and a dropout rate of 27% was reported in the orthokeratology group. In addition, although the OK group had a reduction in axial length over the study 2-year period, corresponding changes in refraction were not reported and the clinical significance of an isolated reduction in axial elongation without refractive changes is not known.

SAFETY

A review by Watt and Swabrick analysed all cases of microbial keratitis (MK) associated with OOK since 2001 to 2007[18]. Not surprisingly, most of the findings remain unchanged from the initial analysis of the first 50 cases[19]. Microbial keratitis raised significant concerns in using OOK lenses. The majority of these infections were central and severe. Two of our own examples can be seen in Figure 1. The final best-corrected visual acuity (BCVA) after resolution of infection was reported in 93 cases, 18% of which had BCVA less than 20/200. Most cases occurred in children or adolescents: 55% of the cases were between 8-15 years old, 41% were between 16-25 years old, and the remaining 4% were above 25 years of age. There is particular concern with OOK in children and young adults since this is the age group with the highest number of users[20]. It would be ideal to stratify the OOK users by age cohorts and analyse the outcomes in terms of initial and final BCVA in order to identify risk factors associated within each cohort, and subsequently with strategies to reduce risk of MK. However, based on the information available related to lens design, material or fitting, lens care and compliance, it was difficult to draw conclusions about risk factors with regards to the specific cohorts by age group. In this review, *Pseudomonas aeruginosa* infection accounted for 37% of the cases while *Acanthamoeba* infection was responsible for 33%. *Acanthamoeba* infection is capable of causing corneal scarring, ultimately leading to a significant vision loss. *Acanthamoeba* infections are known to be associated with contaminated water sources, which further raise the worry regarding the care of OK lenses. Thus it is crucial not to use any tap water during the cleansing of lenses. The prevalence of *Acanthamoeba* related MK is only reported to be 3%-5% in case series for other contact lens wearing modalities. The much higher prevalence of *Acanthamoeba* infection in OOK remains a cause of concern[21,22]. Tear film immunoglobulin A level is found to be reduced in children and may contribute to increased risk of *Acanthamoeba* keratitis in this age group[23]. No significant differences were reported in the ocular flora profile over time in patients

with multiple conjunctival cultures before and during OOK use[24]. It is likely the OOK related MK is related to opportunistic pathogens already present on the corneal surface infecting the underlying compromised corneal epithelial, which resulted from the physical reshaping of the cornea and hypoxic stress from nocturnal wear. Apart from thinning of the cornea, OOK also changes the structural integrity of the epithelium, where the central epithelium significantly differs in cell shape and size. The deeper layers of the cornea may also lose their normal plicae[25,26]. Even with the most oxygen permeable lenses, animal studies found significant *Pseudomonas* adhesions to the cornea with the use of reverse geometry contact lens compared with alignment fit lenses. The enhanced binding is accompanied by thinning and reduced turnover of the epithelium. All these factors may attribute to the increased susceptibility of microbial invasion to the cornea[27]. Clinical trials in human subjects with alignment fit RGP lenses using the highest Dk material did not report an increase in *Pseudomonas* binding after 30 nights of usage[28]. This suggests that the reverse-geometry lens architecture may produce risk of *Pseudomonas* induced MK. The compressive forces of the reverse geometry lenses may lead to disrupted epithelial surfaces, and the reverse geometry lenses may provide a reservoir for bacteria deposition, which is further aggravated by a compromised ocular surface from overnight wear[29,30]. *Pseudomonas* infection is also associated with OOK related corneal ulcer in children. In an observational case series with children, 83% of cases were culture positive for *P. aeruginosa*. Although these ulcers were neither central nor paracentral, all patients suffered a loss in their BCVA with respect to the location of the corneal scar[31]. East Asian ethnicity comprised roughly 95% of the disease population in a review on microbial keratitis associated with OOK[18]. The reported demographic profile could either reflect ethnical susceptibility (as a high proportion of East Asian children are myopic) or could just reflect the demographic profile of the worldwide OK lens wearing population since the usage in more affluent economies[32]. The estimated myopia in urban Chinese children at the age of 18 years would be up to 2.0 dioptres higher than their parents, and their refractive errors at the age of 11 would already be similar to their parents. This suggests a strong environmental effect on myopia development as evident by this remarkable single-generation myopic shift. In addition, the genetic risk factors, and the environmental and lifestyle factors present in the Chinese population may lead to a lower threshold for the Chinese parents to allow their children to wear OK lens[33]. Lin *et al*[34] reported that there is a greater increase in epithelial permeability following overnight contact lens wear in Asian as compared to Caucasian subjects, which could lead to a more easily compromised epithelial barrier, however the rates of MK were not reported to be significantly different from the rest of the world[21]. Further research is warranted to answer whether there is ethnical difference in MK susceptibility.

DISCUSSION

The cases of microbial keratitis associated with orthokeratology were largely documented by the review published in 2007[18]. Since then, we identified another 12 cases *via* our literature search in PubMed[35-39]. Table 1 summarizes the features from the 34 published reports on orthokeratology related microbial keratitis cases up to March 2014[29,31,35-66]. Despite reported case series on MK with OOK, these do not help to determine the true incidence or the relative risks compared with other contact lens modalities. The number of cases reported in the literature likely represents an underestimation, as the values of publications on the same topic become relatively less once a few cases have already been reported in the literature, thus further publication on the same topic is less likely to be accepted by the respective journals, and the incentive for authors to prepare a manuscript also lessens. Without a good estimation of the denominator and numerator, it would be difficult to comment on the absolute risk of microbial keratitis associated with orthokeratology.

Assessment of the risks and adverse effects is limited, as none of the published articles on OOK are level I evidence. Furthermore, the issue on safety could not truly be concluded from the small number of subjects in studies. Adverse effects are often under-reported or inconsistently documented, due to poor indexing, making it more difficult to look up published literature on safety of treatment[67]. The details of reported cases vary in lens type, lens wearing regime, type of lens and compliance to cleansing regime. Despite the credentialing and training programs offered for OOK practices, a learning curve would exist. The interpretation of fluorescein patterns requires skill and experience; the central flat zone of a reverse-geometry contact lens is more discernible to experienced practitioners. Safety about usage and prescription of OOK raises scrutiny. The FDA requires OOK practitioners to be certified to a minimal standard of orthokeratology education and granted the OOK approval without age restriction on the basis that no additional safety concerns are specific to adolescents as long as OOK is fitted by trained personnel and used accordingly[68]. Manufacturers of OOK lenses launched online training program, which consists of certificate course and tests that can be completed in a short period of time. Whether such training program is adequate in providing proper knowledge and skills in the practice of orthokeratology warrants further investigations.

Contact lens use remains the commonest risk factor for microbial keratitis in the paediatric population and orthokeratology is one of the leading causes of contact lens related infection in East Asia[69]. Although many of the cases published have reported data from children, it does not necessary mean that children are at a greater risk of developing MK. Given the potential theoretical benefit in reducing myopia progression, there may be more children using OOK than adults[11]. Due to the larger number of

Table 1 Features of microbial keratitis published in the literature

Ref.	Year of publication	Country of origin	Number of cases	Microbiology
Chen *et al*[40]	2001	Taiwan	1	*Serratia marcescens*
Lü *et al*[41]	2001	China	16	7 = *P. aeruginosa*; 8 = *Acanthamoeba*; 1 = fungus
Chen *et al*[42]	2002	Taiwan	1	*Pseudomonas putida*
Hutchinson *et al*[43]	2002	Australia	2	1 = *P. aeruginosa*; 1 = *Acanthamoeba*, *P. aeruginosa* and *Burkholderia cepacia*
Keddie *et al*[44]	2002	Canada	2	*Acanthamoeba*
Lin *et al*[45]	2002	China	1	*Nocardia sp.*
Lau *et al*[46]	2003	Taiwan	2	*P. aeruginosa*
Poole *et al*[47]	2003	United Kingdom	1	Not identified
Wang *et al*[48]	2003	Singapore	1	*P. aeruginosa*
Xugang *et al*[49]	2003	China	4	*Acanthamoeba*
Young *et al*[29]	2003	Hong Kong	1	*P. aeruginosa*
Hsiao *et al*[50]	2004	Taiwan	7	6 = *P. aeruginosa*; 1 = Not identified
Lang *et al*[51]	2004	United States	2	1 = *P. aeruginosa*; 1 = Not identified
Van Der Worp *et al*[52]	2004	Netherlands	1	*P. aeruginosa*
Young *et al*[31]	2004	Hong Kong	6	5 = *P. aeruginosa*; 1 = Not identified
Araki-Sasaki *et al*[53]	2005	Japan	1	*P. aeruginosa*
Macsai *et al*[54]	2005	United States	2	1 = *P. aeruginosa*; 1 = *H. influenza*
Hsiao *et al*[55]	2005	Taiwan	21	9 = *P. aeruginosa*; 2 = coagulase-negative *Staphylococcus sp.*; 1 = *Serratia marcescens*; 1 = *Acanthamoeba*
Tseng *et al*[56]	2005	Taiwan	10	2 = *Acanthamoeba*; 1 = *P. aeruginosa*; 1 = non fermentative Gram negative bacilli; 6 = Not identified
Wilhelmus *et al*[57]	2005	United States	1	*Acanthamoeba*
Yepes *et al*[58]	2005	Canada	3	1 = *P. aeruginosa*; 1 = *Serratia marcescens*; 1 = *Acanthamoeba*
Lee *et al*[59]	2006	South Korea	1	*Acanthamoeba*
Priel *et al*[60]	2006	Israel	1	*P. aeruginosa*
Sun *et al*[61]	2006	China	28	8 = *P. aeruginosa*; 13 = *Acanthamoeba*; 1 = *Nocardia sp.*; 1 = *Providencia stuartii*; 2 = fungus; 1 = Gram negative rods; 2 = Not identified
Voyatzis *et al*[62]	2006	United Kingdom	1	*P. aeruginosa*
Ying-Cheng *et al*[63]	2006	Taiwan	1	*Burkholderia cepacia*, *Pseudomonas putida*, and *P. aeruginosa*
Lee *et al*[64]	2007	South Korea	4	1 = *Acanthamoeba*; 1 = *Acanthamoeba* and trophozoites; 2 = Not identified
Robertson *et al*[65]	2007	United States	1	*Acanthamoeba*
Watt *et al*[66]	2007	Australia	9	4 = *P. aeruginosa*; 2 = *Acanthamoeba*; 3 = Not identified
Kim *et al*[37]	2009	South Korea	1	*Acanthamoeba* (bilateral)
Shehadeh-Masha'ou *et al*[38]	2009	Israel	4	*P. aeruginosa*
Arance-Gil *et al*[35]	2013	Spain	1	*Acanthamoeba*
Greenwell *et al*[36]	2013	Australia	2	*Acanthamoeba*
Tran *et al*[39]	2014	Australia	4	1 = *Acanthamoeba*; 1 = *P. aeruginosa*; 2 = Not identified

P. aeruginosa: Pseudomonas aeruginosa; H. influenza: Haemophilus influenza; sp: Species.

cumulative years that a child may be exposed to potential risks, complications in children may be reported more frequently than adults. The FDA approval for overnight orthokeratology was based on the premarket study cohort where adolescents aged 12-17 years old comprised 11% of the study sample. In fact, orthokeratology fits represent 28% of all contact lenses prescribed to minors[70]. The FDA issued Section 522 in 2006, requiring manufacturers to conduct post-market surveillance to address "the relative risk of developing MK in persons under the age of 18 as compared to adults in patients undergoing overnight OK treatment". This question was addressed in a retrospective study using a practitioner survey of 1317 OOK patients (51% children)[20]. They found 8 cases of corneal infiltrates associated with a painful red eye (six in children and two in adults). Two were classified as MK and occurred in children, but neither resulted in a loss of visual acuity. The overall estimated incidence of MK is 7.7 per 10000 years of wear (95%CI: 0.9-27.8). For children, the estimated incidence of MK is 13.9 per 10000 patient-years (95%CI: 1.7-50.4). While for adults, the estimated incidence of MK is 0 per 10000 patient-years (95%CI: 0-31.7). This is the largest study to quantify the risk of MK associated with OOK with 2599 patient-years of wears and worthy to note the difference between children and adult rates. Based on the incidence estimated in this study, the two FDA pre-market approval studies[8,71] and another retrospective study of 296 patients by Lipson *et al*[72] did not report any cases of MK. Although the confidence intervals between the adult and children groups overlap, it should not be interpreted as no difference in incidence among the 2 groups as true differences less than 50 cases per 10000 patient-years were beyond the power of that study[20].

CONCLUSION

Although exact incidence of MK associated with OK

lenses is not known, it has the potential to compromise vision. Degree of damage (*i.e.*, reduction in visual acuity) is only one aspect of risk evaluation. In order to maintain the control in myopia, patients have to continue indefinite application of OK lenses overnight. Despite using high oxygen permeable lenses, this will still put the patient at risk of MK, as the reduction of myopia is only temporary without regular overnight application. Comparing OOK with other myopia corrective devices, such as daytime contact lens wear, the risk of infectious keratitis is higher in overnight contact lens wear[73], and there is minimal risk in using spectacle wear. Comparing OOK with LASIK is inappropriate as the latter is an invasive procedure which is not FDA approved for children.

The therapeutic value of overnight orthokeratology remains unclear and many questions remain unanswered, such as the optimal treatment age and duration. Practitioners and end-users of OOK should work together to minimize the risk of MK by reinforcing compliance to proper cleansing techniques and minimizing exposure to contaminated water. OOK users should discontinue lens wear if they feel any pain and seek medical attention immediately. Practitioners must be competent in the prescription of OK lenses through accredited certification courses from appropriate statutory bodies. Better-designed prospective randomized clinical studies are needed to demonstrate the benefit of orthokeratology in reducing myopic progression and to adequately assess their safety, along with the contemporaneous reporting of adverse events. The reported dropout rates of more than 20% in the previous trials also raise concerns regarding tolerability and satisfaction in using OOK. Long-term follow-ups are needed as visual loss related to MK were only encountered in many patients who wore hard contact lens for more than 2 years. The genuine risk of severe MK associated with poor long-term visual outcomes in children needs to be highlighted to parents considering orthokeratology in an effort to avoid preventable visual loss.

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MINIREVIEWS

Advances in surgery procedures for convergence insufficiency-type intermittent exotropia

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Abstract

Intermittent exotropia with convergence insufficiency is defined as a greater exodeviation measured at near than at distance of at least 10 prism diopters and it is harmful to binocular vision at earlier time. This paper mainly introduces three operation patterns including lateral rectus recession(s) with or without a slanting procedure, unilateral lateral rectus recession with medial rectus resection, and medial rectus resection(s) with or without a slanting procedure.

Key words: Intermittent exotropia; Convergence insufficiency; Surgery procedures; Merits and demerits; Deficiency of of prior research

Core tip: Although numerous operation patterns have been developed for intermittent exotropia with convergence insufficiency, there is not a standard protocol. This paper mainly summarizes three operation patterns including lateral rectus recession(s) with or without a slanting procedure, unilateral lateral rectus recession with medial rectus resection and medial rectus resection(s) with or without a slanting procedure. Merits and demerits of different surgery procedures and the deficiencies of different studies are also elucidated in this paper.

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Convergence insufficiency-type intermittent exotropia is defined as a greater exodeviation measured at near than at distance of at least 10 prism diopters[1]. The symptoms of the convergence insufficiency include headaches, asthenopia, difficulty with reading or near tasks and diplopia[2]. In slight cases, symptoms could be alleviated by non-surgical means, such as orthoptic treatment, base-in prism reading glasses, vision therapy and psychotherapy[3,4]. Surgery is reserved for refractory cases that do not respond to these measures or for patients whose deviations are too poorly controlled, or too large at distance or at near to be treatable by nonsurgical means[5]. This review mainly aims to outline the current viewpoints in the surgical interventions to treat convergence insufficiency-type intermittent exotropia. The various surgical treatments for convergence insufficiency-type intermittent exotropia include lateral rectus recession(s) with or without a slanting procedure, unilateral lateral rectus recession with medial rectus resection and medial rectus resection(s) with or without a slanting procedure.

LATERAL RECTUS RECESSION(S) WITH OR WITHOUT A SLANTING PROCEDURE

Raab *et al*[6] conducted bilateral lateral rectus recessions

for exodeviations with different distance-near relationships. Seven patients with exotropia at near 10 prism diopters or more than at distance were treated with the bilateral lateral rectus recession procedure. Only two had a reduction of the near angle to less than 10 prism diopters at the 6 mo follow-up. Yang *et al*[7] conducted a comparative study between bilateral lateral rectus recessions and unilateral lateral rectus recession with medial rectus resection. In their study, the convergence insufficiency-type intermittent exotropia patients were divided into three groups based on patients' response to monocular occlusion and bilateral lateral rectus recessions were performed based on near deviation which was augmented by 1 mm in both eyes. After 2 years, cumulative probabilities of success of bilateral lateral rectus recessions were much lower than those of unilateral lateral rectus recession with medial rectus resection in patients with convergence insufficiency-type intermittent exotropia maintained after monocular occlusion.

In 1999, Snir *et al*[1] proposed slanted lateral rectus recession(s) for the treatment of convergence insufficiency-type exotropia. In their study, the upper horn of the muscle of the patients was recessed according to the distance exodeviation, and the lower horn was recessed according to near exodeviation. Twelve patients underwent slanted lateral rectus recession(s) while six control subjects underwent standard lateral rectus recession(s), and the postoperative follow-up period was 12 mo. Slanted lateral rectus recession(s) decreased the exotropia to < 8 prism diopters in all patients at distance and in 11/12 patients at near. Additionally, the mean difference between the distance and near exodeviation was reduced from 14 prism ± 4.5 prism diopters preoperatively to 2.9 prism ± 2.4 prism diopters postoperatively. All the patients in the control group demonstrated postoperative deviations of < 8 prism diopters at distance, but had residual exodeviations > 8 prism diopters at near. The authors concluded that slanted lateral rectus recession(s) improved the postoperative results and significantly decreased near-distance differences compared with the standard lateral rectus recession(s).

There are very few studies about standard lateral rectus recession(s) and none of them had optimistic results. According to Snir's study[1], it is well known that the effect of slanted lateral rectus recession(s) was better than that of the standard lateral rectus recession(s). However, the sample size in this study was small, and both unilateral lateral rectus recession and bilateral lateral rectus recessions were included. Whether lateral rectus recession(s) with a slanting procedure is useful to convergence insufficiency-type exotropia still needs further research.

UNILATERAL LATERAL RECTUS RECESSION WITH MEDIAL RECTUS RESECTION

Burian *et al*[8] reported that 16 patients with convergence insufficiency were treated by unilateral lateral rectus recession with medial rectus resection. All of their patients had distance exotropia ranging from 10 to 40 prism diopters, whereas at near they ranged from 20 to 40 prism diopters. Surgical amounts were not listed. 81% of these patients had exotropia greater than 10 prism diopters at near, while 38% measured more than 20 prism diopters postoperatively. Only two patients had esotropia at distance at the latest follow-up examination and both measured less than 15 prism diopters.

Kraft *et al*[9] first described an improved unilateral recession-resection surgery biased to medial rectus strengthening more than lateral rectus weakening for treatment of exotropia with convergence weakness, that is, unilateral medial rectus resection based on the near deviation with lateral rectus recession based on the distant deviation. Fourteen patients whose exodeviation at least 8 prism diopters for distance that increased at least 8 prism diopters for near were treated surgically using the procedure. The approach can successfully collapse the near-distance differences while satisfactorily aligning both distance and near fixation.

Choi *et al*[10]conducted this procedure and also found that all 14 patients' distance and near deviation are reduced, and near-distance differences are successfully collapsed from 11.3 to 4.6 prism diopters with a low risk of long-term postoperative esotropia. Besides, Yang and Hwang[7] compared the effect of bilateral lateral rectus recessions and unilateral lateral rectus recession with medial rectus resection, and recommended unilateral lateral rectus recession with medial rectus resection in patients with convergence insufficiency-type intermittent exotropia maintained after monocular occlusion.

Wang *et al*[11] prospectively compared the surgical outcomes of different surgery procedures in children with convergence insufficiency-type intermittent exotropia. The authors concluded the improved unilateral lateral rectus recession with medial rectus resection procedure in which medial rectus resection based on the near deviation with lateral rectus recession based on the distant deviation has a better alignment than the unilateral medial rectus resection and bilateral medial rectus resection surgeries. However, all the three surgery procedures can reduce the near-distance differences.

MEDIAL RECTUS RESECTION(S) WITH OR WITHOUT A SLANTING PROCEDURE

In 1976, Von Noorden[12] reported six patients who underwent bilateral medial rectus resections for exotropia of the convergence insufficiency-type. Four patients decreased in the near exodeviation significantly, but prisms were required to treat postoperative esotropia at distance for several weeks. At final examination, all patients experienced significant symptomatic relief. Hermann[13] also conducted this procedure and all 14 patients showed dramatic relief of severe asthenopic symptoms. Although exoptropia at near would return, occasionally to the origi-

nal angle of deviation, the symptoms did not return.

Kushner[14] performed bilateral medial rectus resections for exotropia of the convergence insufficiency-type in six patients and found an undercorrection rate of 83%, although he did not report the preoperative strabismus angles or dosages of surgery.

Choi *et al*[5] ran a study about bilateral medial rectus resections containing 21 patients. All patients had a history of prolonged difficulties at near work unrelieved by nonsurgical treatment. Unilateral or bilateral medial rectus resection(s) were done with the adjustable suture, which was tied on the first postoperative day, and the mean postoperative follow-up period was 9.1 mo. Postoperatively Fresnel prisms were used temporarily in patients manifesting a consecutive esotropia with diplopia at distance. At the final follow-up examination, patients' mean exodeviation at distance was reduced from 11.4 to -2 prism diopters (esodeviation) and at near, from 25.7 to 3 prism diopters. Their mean near-distance difference was collapsed from 14.3 prism diopters preoperatively to 5 prism diopters postoperatively. In that study, bilateral medial rectus resections with adjustable suture combined with intentional postoperative aggressive overcorrection and the use of Fresnel prisms were effective in intermittent exotropia of the convergence insufficiency-type. The intentional overcorrection during the immediate postoperative period at distance and near was required to prevent long-term undercorrection.

Nemet *et al*[15] first reported that slanted bilateral medial rectus resection was effective in the convergence insufficiency-type exotropia. Because straight-ahead gaze is used mainly for distance vision and downgaze is used mainly for near vision, they recommended the use of slanted resection of the medial rectus muscle, in which the lower margin was resected more than the upper. Biedner[16] reviewed 3 patients who underwent single medial rectus slanting resection. In his study, all 3 patients were aligned to within 10 prism diopters of orthophoria in all fields of gaze without persistent postoperative diplopia and had their asthenopic complaints eliminated. However, Choi *et al*[17] found that medial rectus slanting resection was unsatisfactory in terms of reducing exodeviation and collapsing near-distance differences after long-term follow-up. Ten patients receiving slanted bilateral medial rectus resection were included into their study. The upper edge of the medial rectus was resected according to the distance exodeviation and the lower edge of the medial rectus was resected according to near exodeviation. The medial rectus was reattached at its original insertion after resection. With a mean postoperative follow-up period of 38.9 mo, no patients met the criteria for surgical success and all the patients had recurrent exotropia[17].

The authors who advocated medial rectus with or without a slanting procedure used a diverse amount of resection for a range of near deviations, which made specific surgical dose-response predictions difficult for other surgeons who are faced with this pattern of exodeviation. Therefore, it is not surprising that the postoperative alignments in these patients varied greatly[10].

CONCLUSION

Although numerous operation patterns have been developed for intermittent exotropia with convergence insufficiency, there is not a standard protocol for the disease in the aspect of the design of operation and the evaluation of success rate and clinical outcome. It is necessary to choose an appropriate surgery type, because intermittent exotropia with convergence insufficiency damages binocular vision at earlier time. Future prospective, multicenter and randomize studies with larger samples and longer duration of follow-up are needed to provide reliable evidence to guide the choice of an applicable operation style.

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ORIGINAL ARTICLE

Preoperative intravitreal bevacizumab and silicone oil tamponade for vitrectomy in diabetic retinopathy

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Abstract

AIM: To evaluate the outcomes and complications of vitrectomy for diabetic retinopathy using preoperative bevacizumab and silicone oil (SO) tamponade.

METHODS: Eighty-four eyes (64 patients) that underwent vitrectomy to treat severe proliferative diabetic retinopathy were enrolled in this retrospective, interventional, serial case study. All patients provided signed informed consent preoperatively and the off-label use of bevacizumab was discussed with the patients and confirmed in the signed consent forms. Bevacizumab injections and SO tamponades were used in all cases and intraoperative complications, postoperative complications and postoperative outcomes were analyzed. The primary outcome was the occurrence of intraoperative and postoperative bleeding during and after vitrectomy and SO removal. The secondary outcomes were other complications that occurred during the two surgeries, the surgical time and the postoperative best-corrected visual acuity (BCVA) in logMAR scale compared with the preoperative BCVA in logMAR. The statistical analysis was performed with GraphPad Prism 5 (GraphPad Software, La Jolla, CA) using a column analysis (column statistics and frequency distribution) for the noncomparative analysis and a paired t-test for the comparative study; $P < 0.05$ indicated statistical significance.

RESULTS: Eighty-four eyes of 64 patients were included in the study. Of the 88 eyes initially recruited, 4 eyes (0.45%) developed phthisis bulbi and were excluded from the statistical analysis. Bevacizumab was injected between 1 and 10 d before surgery, with a mean of 3.7 ± 2.2 d. Forty-six eyes (54.8%) had no complications during the surgery; 6 eyes (7.1%) had vitreous hemorrhage; 21 (25%) had a single retinal tear; 7 (8.3%) had two or more retinal tears, one of which was in the posterior pole, temporal to the fovea; 2 (2.4%) had retinal tears associated with hemorrhage; 1 (1.2%) had choroidal detachment; and 1 eye (1.2%) had dialysis in the temporal entrance of the trocar. After the surgery and SO removal, 60 eyes (71.4%) had no complications, 8 (9.5%) had vitreous hemorrhage, 2 (2.4%) had a macular hole, 2 (2.4%) had an epiretinal membrane, 7 (8.3%) had rhegmatogenous retinal detachment, 2 (2.4%) had neovascular glaucoma, 2 (2.4%) had a corneal trophic ulcer, and 1 (1.2%) had central venous occlusion. The surgical time ranged from 40 to 120 min, with a mean of 77.8 ± 20.7 min. The final status of the lens was 34 phakic eyes (40.5%) and 24 pseudophakic eyes (28.5%); in 26 eyes (31%), the lens was extracted via phacoemulsification combined with vitrectomy or SO removal. The preoperative BCVA in logMAR ranged from 0.1 to 3.0, with a mean of 1.6 ± 0.9; the postoperative BCVA in logMAR ranged from 0.0 to 3.0, with a mean of 0.9 ± 0.7; the preoperative and postoperative

BCVA values were significantly different ($P < 0.0001$).

CONCLUSION: Bevacizumab may diminish intraoperative and postoperative bleeding, thus possibly facilitating intraoperative maneuvers, diminishing the complications and playing a role in the final outcomes of these eyes.

Key words: Bevacizumab; Diabetic retinopathy; Vitrectomy; Silicone oil; Vitreous hemorrhage

Core tip: Our findings are in agreement with previously published reports of the importance of intravitreal bevacizumab (IVB) injections in severe or complex cases of diabetic retinal detachment. These very difficult cases, when performed without the use of IVB, have high rates of intraoperative and postoperative bleeding and a worse final outcome. The strengths of our work include the average follow-up period of 33.90 ± 22.97 mo (range: 6-84 mo) and the number of eyes (84) subjected to surgery during this period. The weaknesses of our study are that it was retrospective and lacked a control group.

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INTRODUCTION

The primary goal of diabetic vitrectomy is the restoration of vision. To achieve this goal, we remove the vitreous blood, reattach the macula and retina where traction is present, and remove any cataracts that are present. The second and extremely important aim of surgery is to control the diabetic neovascularization process to promote long-term anatomic and visual success. Diabetic patients undergo surgery consisting of core vitrectomy; the removal of the posterior hyaloid as far as the retinal detachment area, which is then dissected using delamination, segmentation, bimanual or *en bloc* techniques or combined procedure; the endophotocoagulation of the ischemic retina; and, in the majority of cases, the use of a tamponade, which could be gas (sulfur hexafluoride or perfluoropropane) or silicone oil (SO)[1-3]. When these surgical objectives are achieved and the 6 mo outcome is good, the eyes tend to remain stable for many years[1,4,5]. Tractional retinal detachment (TRD) involving the macula and nonclearing vitreous hemorrhage are the most common indications for diabetic vitrectomy[1]. Intraocular hemorrhage is a serious event during diabetic vitrectomy. Extensive hemorrhage may prevent the successful conclusion of surgery and may increase intraoperative complications. The removal of clotted blood may not only extend a preexisting retinal break but may also create new retinal breaks[6-8].

The most common indication for reoperation after diabetic surgery is recurrent vitreous hemorrhage. Approximately 60% of eyes develop recurrent vitreous hemorrhage sometime in the postoperative period[9]. Hemorrhage usually occurs within the first few days after surgery but may occur months or years later. Two-thirds of all hemorrhages occur during the first 6 mo[10]. Various surgical maneuvers have been utilized to prevent intraoperative vitreous hemorrhaging, such as increasing the intraocular pressure (IOP) by increasing the infusion of balanced salt solution (BSS), using the vented gas forced infusion (VGFI) setting on the vitrectomy machine, and using endodiathermy or perfluorocarbon as a surgical tool to stop the bleeding[11]. Bevacizumab (Avastin, Genentech Inc., San Francisco, CA), a full-length humanized monoclonal antibody against vascular endothelial growth factor (VEGF), was approved by the US Food and Drug Administration for the treatment of metastatic colorectal cancer[12-14]. Recent reports have indicated that intravitreal bevacizumab (IVB) injections show promise for targeting the VEGF-implicated intraocular neovascularization associated with age-related macular degeneration[15] and proliferative diabetic retinopathy (PDR)[16]. IVB has recently been shown to enhance the clearance of vitreous hemorrhage and to induce the involution of both retinal neovascularization[16,17] and anterior segment neovascularization[16,18,19]. Recently, numerous studies have reported the clinical outcomes of IVB applied as an adjunct to vitrectomy in the management of diabetic retinopathy. Bevacizumab can induce the regression of retinal neovascularization in patients with diabetes; therefore, it has been suggested that the presurgical administration of IVB might reduce intraoperative bleeding during vitrectomy for PDR[20]. However, the presurgical administration of IVB remains controversial[21]. Some studies have reported that bevacizumab pretreatment for diabetic vitrectomy did not influence the rates of postoperative vitreous hemorrhage or final visual acuity (VA). Although many surgeons perform IVB before vitrectomy in patients with diabetes, there are limited systematic studies or studies with large sample sizes demonstrating the benefits of IVB in facilitating surgery and improving clinical outcomes[21]. A systematic review and meta-analysis of clinical outcomes of vitrectomy with or without IVB pretreatment for severe diabetic retinopathy revealed that IVB injection before vitrectomy for PDR could reduce intraoperative bleeding, the frequency of endodiathermy, the mean surgical time, the reabsorption time of blood after vitrectomy and the incidence of recurrent vitreous hemorrhage (VH), as well as improving the best-corrected visual acuity (BCVA)[21].

Despite the success of pars plana vitrectomy (PPV) in managing the severe complications of diabetic retinopathy, significant operative and postoperative complications still occur and may lead to anatomical failure and blind-

ness. The recurrence of retinal detachment secondary to fibrovascular proliferation, progression of neovascularization with neovascular glaucoma, hypotony with subsequent phthisis bulbi, and fibrinoid syndrome are some of the many reported postoperative complications of diabetic vitrectomy. SO facilitates retinal reattachment by providing extended intraocular tamponade[22]. Oil may compartmentalize the eye and may play a role in inhibiting progressive neovascularization in the anterior segment by preventing the diffusion of angiogenic substances. In addition, SO can prevent hypotony and subsequent phthisis bulbi[23]. Castellarin *et al*[3] demonstrated the effectiveness of SO tamponade in cases of severe diabetic retinopathy.

MATERIALS AND METHODS

A retrospective interventional serial case study was performed on 84 eyes of 64 patients who underwent vitrectomy for severe diabetic retinal detachment at Holhos Uberlandia Eye Hospital between March 2007 and August 2013. The same surgeon (MAF) performed all of the surgeries. The possible risks and benefits of the treatment were explained to the patients before surgery, as was the off-label use of IVB. Informed consent was obtained before the procedures, in accordance with the Helsinki Declaration. Approval to review the patient data was obtained from the institutional review board. All patients underwent a complete ophthalmological examination with refraction, slit lamp examination, IOP measurement, fundus photography and fluorescein angiography, if possible. Additionally, ultrasound was performed in cases where the fundus could not be examined because of a cataract, vitreous hemorrhage or any other condition that obscured the fundus. Preoperative data were obtained from the final examination before surgery and intraoperative data were collected from the surgical description. Postoperative data were collected one day, one week and monthly after the surgery and data were also collected after SO removal, except for VA measurements which were performed before the surgery and at least one month after the SO removal. After surgery, the patients were instructed to return in the event of complications such as pain, decreased vision or any changes; otherwise, they returned on the following appointment date. The BCVA was measured using the Snellen chart and VA was converted to a logMAR score for analysis. All patients received a preoperative 1.25-mg IVB injection (Avastin, Genentech Inc.) and underwent 23-gauge transconjunctival sutureless vitrectomy using the Accurus vitrectomy machine (until January 2012) and the CONSTELLATION machine (after that period) (Alcon, Fort Worth, TX) and 1300-centistokes SO tamponade (Bausch and Lomb, Rochester, NY). Intraoperative complications, postoperative complications and postoperative outcomes were analyzed. The primary outcome was intraoperative and postoperative bleeding occurring during and after vitrectomy and SO removal. The secondary outcomes were any other complications that occurred during and after the two surgeries, the surgical time, the status of the lens and a comparison of the preoperative and postoperative BCVA values in logMAR. The statistical analysis was performed with GraphPad Prism 5 (GraphPad Software, La Jolla, CA) using a column analysis for the non-comparative analysis and Student's paired t-test for the comparative study; $P < 0.05$ was considered statistically significant.

RESULTS

At the beginning of the chart review, 88 eyes of 68 patients met the inclusion criteria; however, 4 eyes (0.45%) developed phthisis bulbi during the follow-up period and were excluded from the statistical analysis. Thus, 84 eyes of 64 patients were included in the study. Forty-two patients were male (65.6%), and 22 (34.4%) were female. All the patients had severe or complicated diabetic retinal detachment. Three of 84 eyes (3.6%) had severe TRD; six patients (7.1%) had combined tractional and rhegmatogenous retinal detachment; and 75 (89.3%) had tractional retinal detachment with some degree of vitreous hemorrhage (Figures 1 and 2). The patients' ages ranged from 30 to 86 years, with a mean ± SD of 61.25 ± 12.29 years. Bevacizumab was injected between 1 and 10 d before surgery, with a mean ± SD of 3.7 ± 2.2 d. Forty-six eyes (54.8%) had no complications during the surgery; 6 (7.1%) had vitreous hemorrhage; 21 (25%) had one retinal tear; 7 (8.3%) had two or more retinal tears, one of which was in the posterior pole, temporal to the fovea; 2 (2.4%) had a retinal tear associated with hemorrhage; 1 (1.2%) had choroidal detachment; and 1 (1.2%) had dialysis in the temporal entrance of the trocar (Figure 3). For the six patients (7.1%) who had hemorrhage during the vitrectomy, the hemorrhage was confined to the area between the SO and retina and the blood was reabsorbed in 30-90 d. In two other patients (2.4%), the hemorrhage occurred in the tear location and was also confined to the area between the SO and retina; the blood was reabsorbed in 90 and 120 d. The time until the removal of the SO ranged from 1 to 8 mo, with a mean ± SD of 4.16 ± 1.59. All patients had attached retinas and none had a vitreous cavity or preretinal hemorrhage before SO removal. During the postoperative period after SO removal, 60 eyes (71.4%) had no complications, 8 (9.5%) had vitreous hemorrhage, 2 (2.4%) had a macular hole (MH), 2 (2.4%) had an epiretinal membrane (ERM), 7 (8.3%) had rhegmatogenous retinal detachment, 2 (2.4%) had neovascular glaucoma, 2 (2.4%) had corneal trophic ulcers, and 1 (1.2%) had central venous occlusion (Figure 4). In the group that presented with vitreous hemorrhage after SO removal, 8 (9.5%) patients were followed for at least one month and were reoperated if the hemorrhage did not improve during this period. Five patients improved over periods varying from 30 to 60 d, and three patients were reoperated after 30 d of no improvement. In the patients who were reoperated, a new IVB injec-

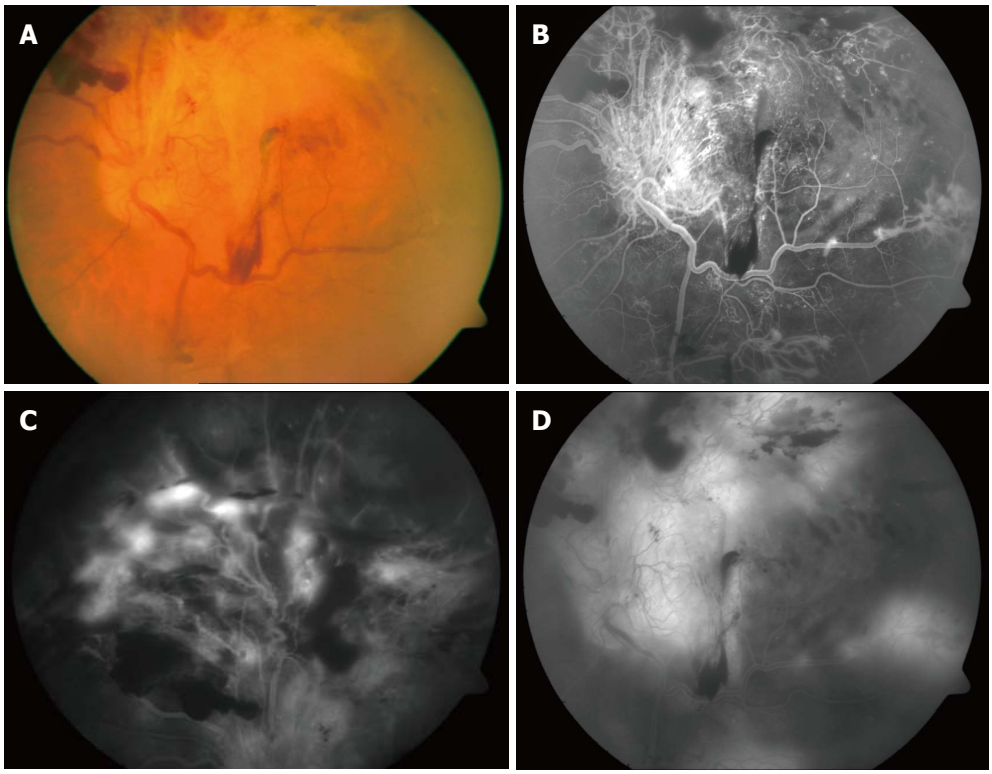

Figure 1 Preoperative images of the retina showing diabetic retinal detachment involving the posterior pole (A), the superior retina (B), and the region near the arcade (C), as well as subhyaloid and preretinal hemorrhage in the equator (D).

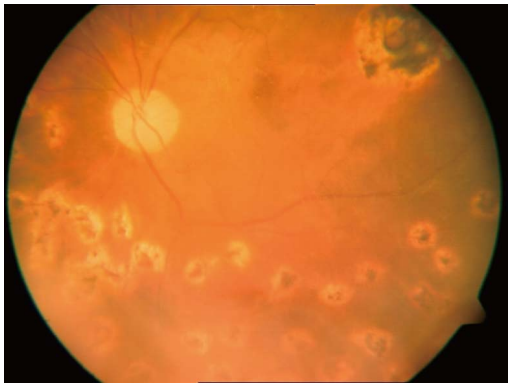

Figure 2 Postoperative image of the retina after silicone oil removal showing the retina attached and the posterior pole retinal tear treated with a laser.

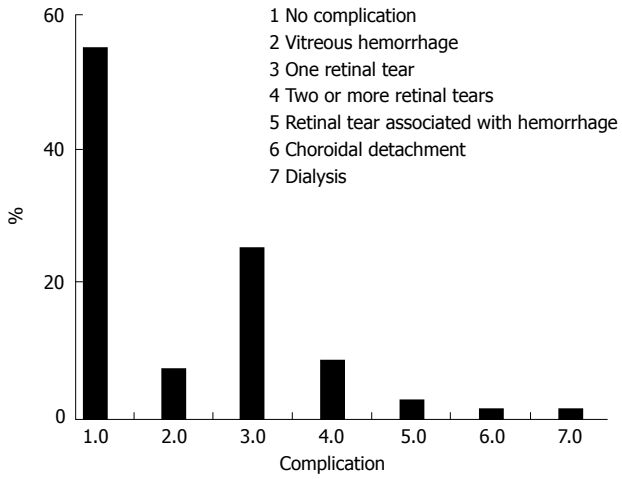

Figure 3 The percentage of intraoperative complications.

tion was performed after the vitrectomy was completed. These patients did not present with rebleeding. Two patients (2.4%) had an MH that developed subsequently, after SO removal (1 year and 11 mo and 2 years and 5 mo). These patients were reoperated with the closure of the MH, using SF_6 gas as a tamponade. Seven patients (8.3%) who had rhegmatogenous retinal detachment were reoperated to attach the retina; the retina remained attached until the final follow-up. The 2 (2.4%) patients who had ERM were reoperated with a good anatomic aspect of the macula. The two patients who presented with neovascular glaucoma were treated with the injection of 1.25 mg of bevacizumab into the anterior chamber and vitreous cavity as well as with the topical administration of brimonidine tartrate, timolol maleate, dorzolamide hydrochloride, atropine and prednisolone acetate. The IOP of one patient was controlled; the other patient underwent glaucoma surgery. The surgical time ranged from 40 to 120 min, with a mean of 77.8 ± 20.7 min. The follow-up ranged from 6 to 84 mo, with a mean of 33.90 ± 22.97 mo. The final status of the lens was 34 phakic eyes (40.5%) and 24 pseudophakic eyes (28.5%); in 26 eyes (31%), the lens was removed during vitrectomy or SO removal. The preoperative BCVA in logMAR ranged from 0.1 to 3.0, with a mean of 1.6 ± 0.9; the postoperative

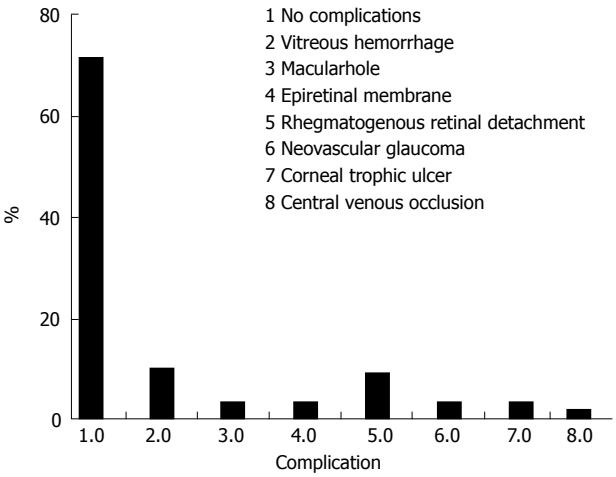

Figure 4 Histogram showing postoperative complications: Frequency distribution.

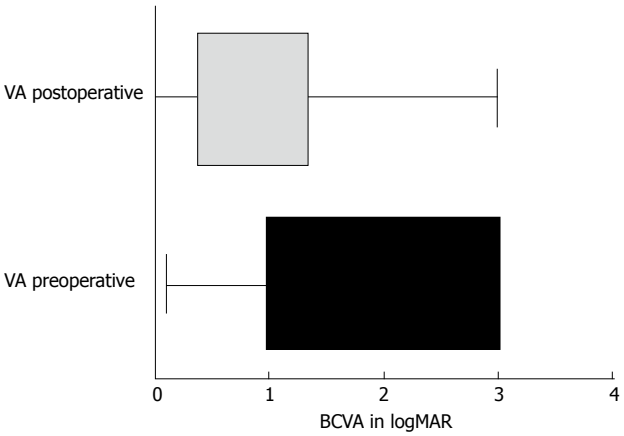

Figure 5 Comparison of pre- and postoperative visual acuity: Horizontal box-and - whiskers plot. VA: Visual acuity; BCVA: Best-corrected visual acuity.

BCVA in logMAR ranged from 0.0 to 3.0, with a mean of 0.9 ± 0.7; the preoperative and postoperative BCVA values were significantly different ($P < 0.0001$) (Figure 5).

DISCUSSION

Bevacizumab is a recombinant humanized monoclonal anti-VEGF antibody that is used to induce the regression of neovascularization and to reduce permeability of the vessels[24]. Bevacizumab is increasingly used to treat choroidal neovascularization and diabetic macular edema[25,26] and it has proven to be effective for the treatment of PDR complicated by vitreous hemorrhage[16,27,28]. In one study, the results of fluorescein angiography revealed a reduction in the leakage from the foci of neovascularization and the regression of the neovascular component of the fibrovascular tissue in eyes with PDR within 1 wk after IVB. Based on these observations, it was suggested that IVB may reduce the incidence of intraoperative hemorrhage during diabetic vitrectomy[29]. Chen first reported that IVB was helpful in facilitating vitrectomy for severe PDR[17]. Many clinical trials have shown that IVB before vitrectomy improves the condition of the fundus. In a study by Ahmadieh, preoperative IVB injection led to a significant resolution of VH and improvement of vision in nine eyes (25.7%) initially scheduled for vitrectomy to the degree that surgical intervention was no longer required[30].

Based on surgeons' experience, the regression of the vascular component of the fibrovascular complexes after IVB facilitates the segmentation and delamination of membranes[31]. This result is due to the membranes being less adhesive to the underlying retina and being readily separated from the retina. The hemodynamic changes in retinal circulation that occur after IVB, such as constriction and decreased flow in new vessels, greatly reduce the likelihood of intraoperative bleeding. The analysis of our study's primary outcome revealed that only 6 of 84 eyes (7.1%) had hemorrhage during the primary vitrectomy and 2 eyes (2.4%) had a retinal tear associated with hemorrhage at the location of the tear. Our study included 84 eyes; the majority of previously published studies had smaller numbers of patients[11,31-33]. Rizzo *et al*[11] observed mild intraoperative bleeding in 3 of 11 cases of PPV with IVB (PPV + IVB) and in 7 of 11 cases of PPV without IVB (PPV alone); they also reported severe intraoperative bleeding in 2 of 11 PPV+ IVB cases and 9 of 11 PPV alone cases. El-Batarny observed 6.8 ± 1.5 bleeding attacks/patient (range: 4-9) in 15 cases of PPV alone and 1.9 ± 1.1 bleeding attacks/patient (range: 0-4) in 15 cases of PPV + IVB[33]. In a systematic review and meta-analysis of the clinical outcomes of vitrectomy with or without IVB pretreatment for severe diabetic retinopathy, Zhao *et al*[21] found that IVB injection before vitrectomy for PDR reduced intraoperative bleeding, the frequency of endodiathermy and the mean surgical time. The above studies demonstrate that IVB is an important tool for reducing intraoperative bleeding and facilitating intraoperative surgical maneuvers, which is consistent with our findings. In the present work, postoperative bleeding after vitrectomy was confined to the area between the retina and the SO, which is in agreement with the findings of Castellarin *et al*[3] and Yeh *et al*[31].

Our surgical time ranged from 40 to 120 min, with a mean of 77.8 ± 20.7 min. This time was longer than that reported by El-Batarny[33] and Rizzo *et al*[11] for PPV associated with IVB. However, our study was retrospective and our surgical time was calculated from the anesthesiologist's records and was most likely overestimated. The surgical time reported by El-Batarny was 61.6 ± 14.5 min (range: 40-90 min) in the PPV + IVB group[33]. Rizzo *et al*[11] reported a mean surgical time of 57 ± 9 min in the PPV+ IVB group. The diabetic retinal detachment in our study had a simple classification compared with the "Elliott" grading system used by Yeh *et al*[31] but most papers do not classify diabetic retinal detachment using this classification; as a result, comparing the cases would be impossible. Our study was limited to patients with TRD that encompassed a broad area; that threatened or involved the macula; that was or was not associated with vitreous hemorrhage; that varied in degree from mild, only in the

inferior retina, to massive, involving the vitreous and subhyaloid spaces; and that sometimes covered the posterior pole or extended to close to the arcades. We also had several patients with combined retinal detachment. Our study included 3 eyes (3.6%) with severe TRD, six eyes (7.1%) with combined tractional and rhegmatogenous retinal detachment and 75 eyes (89.3%) with TRD with some degree of vitreous hemorrhage. After SO removal, 8 eyes (9.5%) had rebleeding; these were followed for at least one month and were reoperated if the hemorrhage did not improve in this period. Five patients improved over periods varying from 30 to 60 d, and three eyes (3.6%) were reoperated after 30 d of no improvement. In these patients, a new IVB injection was performed after the completion of the vitrectomy and rebleeding did not occur. Our rate of rebleeding after SO removal was low at 9.5% and only three patients (3.6%) had to undergo reoperation. El-Batarny reported a postoperative bleeding rate of 26.6% in the PPV group and none in the PPV + IVB group; however, there were only 15 patients in each group. We followed our patients for an average of 33.90 ± 22.97 mo (range: 6-84 mo); our follow-up period was long because we performed a single retrospective study with data collection beginning in March of 2007. This follow-up period was much longer than those of other studies which had follow-ups of approximately 6 mo[21]. We had 21 eyes (25%) with one retinal tear, 7 eyes (8.3%) with two or more retinal tears, 2 (2.4%) with retinal tears associated with hemorrhage and 1 case (1.2%) with dialysis in the temporal entrance of the trocar. We had 31 eyes with iatrogenic retinal tears (36.9%), a higher number than in other reports. Rizzo *et al*[11] reported 4/11 iatrogenic retinal tears in the PPV alone group and none in the PPV + IVB group. El-Batarny[33] reported iatrogenic breaks in 6 cases (40%) in the PPV alone group and in 3 cases (20%) in the PPV + IVB group. In the present work, the preoperative BCVA in logMAR ranged from 0.1 to 3.0, with a mean of 1.6 ± 0.9, and the postoperative BCVA in logMAR ranged from 0.0 to 3.0, with a mean of 0.9 ± 0.7; the preoperative and postoperative values were significantly different ($P < 0.0001$). Similar findings were reported by Zhao *et al*[21] in a meta-analysis of preoperative IVB for diabetic vitrectomy.

In conclusion, IVB may diminish intraoperative and postoperative bleeding, thus possibly facilitating intraoperative maneuvers, diminishing the complications in these very complex cases and playing a role in the final outcomes of these eyes. The postoperative bleeding in the SO-filled eyes was confined to the area between the retina and SO; therefore, SO may act as a secondary tool to prevent postoperative bleeding. Additional prospective studies with control groups and larger numbers of eyes will be necessary to confirm these hypotheses.

COMMENTS

Background

Retinal detachment is an important cause of visual impairment and blindness in diabetic patients; to treat these cases, the authors performed vitrectomy. In such cases, bleeding during vitrectomy is very common; for the vitrectomy to be successful, the surgeon must stop the bleeding. The intravitreal injection of bevacizumab (Avastin), a monoclonal antibody against vascular endothelial growth factor (VEGF), is used to prevent or decrease bleeding during the surgery, thus facilitating surgical maneuvers.

Research frontiers

Intravitreal bevacizumab (IVB) has been used for many conditions, including metastatic colon cancer and ocular conditions associated with VEGF, such as aged-related macular degeneration (ARMD), diabetic macular edema, retinal vein occlusion and proliferative diabetic retinopathy (PDR). Based on these findings, the use of Avastin to stop or decrease bleeding during vitrectomy in diabetic patients has become popular among retinal specialists.

Innovations and breakthroughs

This study in which a large number of patients were followed for long time after vitrectomy demonstrated that the use of Avastin is very promising in these cases because it decreases bleeding during and after surgery, which in turn facilitates the procedure and the surgical maneuvers by allowing the physician to operate in a clear medium, resulting in better postoperative outcomes.

Applications

These results suggest that Avastin should be prospectively compared to a sham or placebo in a large group, such as that in our study, to provide an evidence-based demonstration of the efficacy of this antibody.

Terminology

VEGF, or vascular endothelial growth factor, is directly involved in the neovascularization that occurs during pathological processes in the eye, such as ARMD and PDR. Bevacizumab is an antibody against VEGF, or an anti-VEGF antibody, which inhibits or blocks the growth of new vessels.

Peer review

The manuscript is a retrospective review. The only novel point is the long-term follow up.

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RETROSPECTIVE STUDY

Cumulative probability and risk analysis for Nd:YAG laser capsulotomy

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Abstract

AIM: To estimate the cumulative probability of Nd:YAG capsulotomy at a teaching institution and evaluate secondary risk factors.

METHODS: The records of all patients who underwent phacoemulsification with intraocular lens (IOL) placement between 2005-2010 were retrospectively reviewed. The cumulative probability of Nd:YAG capsulotomy (capsulotomy) was calculated using Kaplan-Meier survival analysis and secondary risk factors were evaluated using the Cox proportional hazards regression model.

RESULTS: One thousand three hundred and fifty four charts were reviewed. A total of 70 capsulotomies were performed. The mean follow-up was 19.4 mo (standard deviation 17 mo). The cumulative probability of capsulotomy was 4% at 1 year, 5% at 2 year, and 9% at 3 year. Multivariate analysis demonstrated an increased risk with younger age (HR = 1.03, CI 1.01-1.05, P = 0.007), placement of sulcus IOL (HR = 2.57, CI 1.32-4.99, P = 0.005), ocular trauma (HR = 2.34, CI 1.13-4.83, P = 0.02), and phacoemulsification by a more experienced surgeon (HR = 4.32, CI 1.89-9.87, P = 0.001).

CONCLUSION: Cumulative probability of capsulotomy was lower than previously reported. Posterior capsule opacification was strongly associated with younger age and factors associated with high-risk cataract surgery. Surgeon awareness to the risk factors that correlate with posterior capsulotomy may allow for more thorough pre-operative disclosure and enhance patient satisfaction.

Key words: YAG capsulotomy; Posterior capsule opacification; Cataract surgery; Risk factor; Surgeon experience; Cumulative probability; Teaching institution

Core tip: Posterior capsule opacification (PCO) is a known late sequelae of cataract surgery. Our study uncovers risk of PCO in teaching institutions is associated with surgeon experience in that YAG capsulotomy rates are higher in patients whose cataract surgery was performed by a more experienced surgeon. Capsulotomy rates overall were lower than previously reported.

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INTRODUCTION

Posterior capsule opacification (PCO) is the most common late sequelae after cataract surgery. Its definitive treatment, Nd:YAG laser posterior capsulotomy poses a financial burden on health care systems worldwide and causes rare, but serious patient morbidity[1,2]. Identifying the incidence and risk factors for PCO is important, not only for prevention, but also to provide patients with better pre-operative disclosure of the late changes possible after cataract surgery.

The cumulative probability of capsulotomy after phacoemulsification ranges between 1.95% and 11.8% at one year[3-5] and increases to 18.5% to 20.7% at three year. Independent and well established risk factors for capsulotomy include younger age at the time of cataract extraction and intraocular lens (IOL) properties[6,7]. A metaanalysis evaluating 66 prospective randomized controlled clinical trials comparing poly-methylmethacrylate (PMMA), hydrogel, hydrophobic acrylic and silicone IOLs did not detect a significant influence of IOL material on PCO incidence. In contrast, sharp edged IOL optics had a significantly lower incidence of PCO compared to round edged IOL optics. Haptic design, whether one-piece or three-piece IOLs did not bear influence on PCO incidence. Johansson *et al*[8] reported a cumulative incidence of capsulotomy five year after cataract extraction with IOL placement in the capsular bag of 17% with sharp-edged hydrophobic acrylic IOLs, 24% with round-edged hydrophobic acrylic IOLs, and 30% with sharp-edged hydrophilic acrylic IOLs. Additionally, they observed that patients surviving the five year study were more likely to have had capsulotomy. Along with modern IOL design and evolution in surgical technique, from extracapsular cataract extraction to small incision phacoemulsification, capsulotomy rates have declined since. While it is encouraging that the incidence of capsulotomy appears to be decreasing the reported rates in the literature cannot be extrapolated to a patient population at a teaching institution.

This study sets out to evaluate the influence of surgeon experience on PCO incidence. Prior studies evaluating the influence of surgical experience on PCO did not further differentiate data by year of training[6]. While patients may be stratified at the time of preoperative evaluation to match eyes more prone to intraoperative challenges with more experienced surgeons at a teaching institution prior trauma is commonplace among veterans as most were experienced some trauma during training and service. Likewise, intraoperative floppy iris syndrome and the ubiquitous intake of alpha adrenergic for benign prostate hyperplasia in the veteran population cannot be avoided by a novice surgeon in this population. Given the uniform patient population and identical surgical technique this study is uniquely positioned to evaluate the cumulative incidence of capsulotomy and associated risk factors including any influence of year of training.

MATERIALS AND METHODS

After receiving institutional review board approval, the medical records of 1354 patients who underwent cataract extraction at the Veteran Affairs Hospital in Miami, Florida between 2005 and 2010 were retrospectively reviewed. Patients who underwent phacoemulsification with IOL placement in the capsular bag, ciliary sulcus, or anterior chamber were included in the review. Patients with anterior capsule tear, posterior capsule tear, anterior or posterior vitrectomy were included. Patients with concomitant unrelated surgery (corneal transplant, trabeculectomy, glaucoma drainage device, epiretinal membrane peel, endolaser) were included. Eyes that underwent intraoperative conversion to manual extracapsular cataract extraction were excluded. For patients who underwent sequential cataract extraction, only the first eye was included in the analysis.

The following information for each patient was recorded: age at surgery; date of surgery; date of capsulotomy; date of last visit; gender; ethnicity; history of diabetes, glaucoma, ocular trauma, and uveitis; intraoperative anterior vitrectomy, pars plana vitrectomy, concomitant glaucoma surgery, posterior capsule rupture; experience level of primary surgeon; and IOL model (SN60WF (hydrophobic acrylic, sharp-edged, 1-piece), MA60AC (hydrophobic acrylic, round-edged, 3-piece), SN60T/SN6AT (hydrophobic acrylic, sharp-edged, 1-piece), and MTA (PMMA, convexoplano, 1-piece).

Surgeries were performed by an ophthalmology team, which included an attending surgeon and a second year ophthalmology resident [post-graduate year (PGY) 3], or a third year ophthalmology resident (PGY4), or by an attending surgeon (PGY5 or greater) and assistant surgeon in training. Patients were preoperatively stratified and patients with a phacodonesis due to ocular trauma, prior eye surgery, monocular patients, pseudoexfoliation of the lens, pupil dilation less than 6 mm, corneal opacity, and endothelial guttatae were operated by a PGY4 or higher level surgeon. After routine postoperative follow-up at one day, one week, and one month after surgery with their primary surgeon, patients were followed every six to twelve months. The indications for capsulotomy were driven by patients' symptoms (decreased visual acuity, decreased contrast sensitivity, or significant glare) with objective evidence of PCO. The final decision for capsulotomy was made by an attending physician.

The cumulative probability of capsulotomy was calculated by Kaplan-Meier survival analysis. The Cox proportional hazards regression model was used to evaluate potential risk factors including: age; gender; ethnicity; diabetes; glaucoma; ocular trauma, uveitis, anterior vitrectomy, pars plana vitrectomy, concomitant glaucoma surgery; posterior capsular rupture; IOL type, IOL placement; and surgeon experience.

RESULTS

Table 1 displays the patient's demographic and clinical

Table 1 Patient demographics and pre-operative and operative clinical information

Number eyes (patients)	1354 (1354)
Age at time of cataract surgery, mean ± SD (*n*)	69 ± 10 (1354) range 38-94
Months follow-up, mean ± SD	19.4 ± 17 mo
Gender, % male (*n*)	97 (1318)
Ethnicity	
% White, non-Hispanic (*n*)	63 (315)
% Black, non-Hispanic	23 (113)
% White, Hispanic	14 (68)
Diabetes, % yes (*n*)	35 (477)
Glaucoma, % yes (*n*)	33 (452)
Ocular trauma, % yes (*n*)	5 (62)
Uveitis, % yes (*n*)	4 (57)
Selected lens type, % (*n*)	
Monofocal, 3-piece (MA60)	29 (389)
Monofocal and toric, 1-piece (SN60, SN6A)	69 (937)
Anterior chamber lens (MTA)	1.6 (22)
Surgeon level, % (*n*)	
PGY2 surgeon	56 (757)
PGY3 surgeon	33 (437)
PGY5 or higher (Experienced surgeon)	11 (148)
Sulcus lens placed, % (*n*)	6.6 (89)
Anterior vitrectomy performed, % (*n*)	4 (54)
Planned Pars Plana Vitrectomy performed, % (*n*)	4 (51)
Unplanned Pars Plana Vitrectomy performed, % (*n*)	1 (10)
Concomitant glaucoma surgery	2.7 (36)
Posterior capsular rupture	2.9 (39)

Experienced surgeon: Attending.

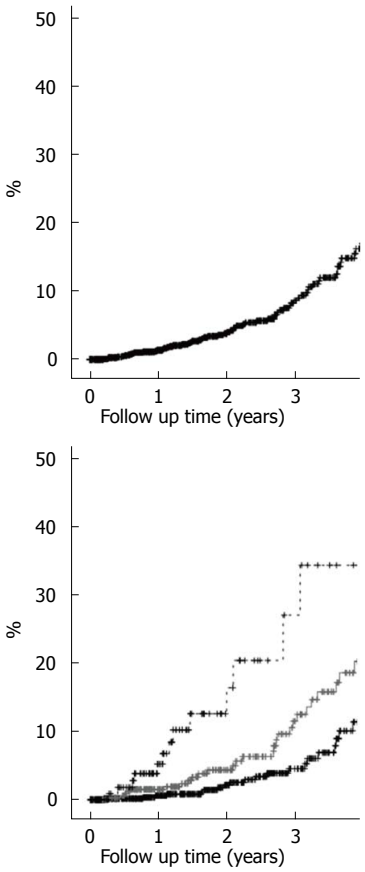

Figure 1 Kaplan-Meier analysis. A: Kaplan-Meier analysis of the cumulative probability of capsulotomy; B: Kaplan-Meier analysis of the cumulative probability of capsulotomy in eyes operated on by post-graduate year (PGY) 3 surgeons, PGY4 surgeons, and experienced surgeons (PGY5 and higher).

information. 1354 cataract extractions with phacoemulsification and IOL placement were included in the study with a total of 70 capsulotomies performed after a mean follow-up of 19.4 mo (SD 17 mo). The cumulative probability of capsulotomy in our population was 4% at 1 year, 5% at 2 year, and 9% at 3 year (Figure 1A).

Table 2 displays the variables found to significantly increase the likelihood of capsolotomy. Younger individuals were at increased risk for capsulotomy compared to older individuals. Sulcus IOL placement portended an approximate 2.5 fold increased risk for subsequent capsulotomy. Clinical signs of ocular trauma increased the risk of capsulotomy 2.3 fold. Increasing surgeon experience increased the risk of capsulotomy with a 2.39 fold increased risk for PGY4 surgeons and a 4.32 fold increased risk for PGY 5 and above surgeons. The three year capsulotomy rate for PGY3/attending teams was 4%, for PGY4/attending teams was 13%, and for PGY5/attending teams was 24% (Figure 1B). Factors not found to affect the risk of capsulotomy included patients', ethnicity, and comorbidities such as diabetes, glaucoma, concomitant glaucoma surgery, uveitis, intraoperative anterior vitrectomy, pars plana vitrectomy, posterior capsule rupture, shape or material of the IOL.

DISCUSSION

We found a cumulative probability of capsulotomy after phacoemulsification of 4% at 1 year, 5% at 2 year, and 9% at 3 year. The highest level of evidence describing the probability of capsulotomy after cataract extraction is provided in a meta-analysis of 49 studies that reported a 20.7% cumulative probability of capsulotomy at three year[9]. While it is encouraging that the capsulotomy rate at our institution is much lower at three year, it is important to consider that the metaanalysis included patients who underwent traditional extracapsular cataract extraction, a surgical technique known to be associated with a higher risk of PCO formation. However, studies evaluating PCO incidence after phacoemulsification found similarly high rates of PCO, at 18.5% cumulative probability of capsulotomy after 3 year[3].

Differences in population demographics and lens choice may partially explain differences between published capsulotomy rates. The surgical population at the Veterans Affairs Hospital was younger with a mean age of 69 ± 10 year compared to 76.7 year and 74 year in other studies[4,8]. Our data confirms that younger age is an independent risk factor for capsulotomy. Female patients may carry a higher rate of capsulotomy[6]. Given that 97% of our patients were men our data may be skewed towards a lower incidence of capsulotomy. However, we could not confirm prior studies showing an advantage

Table 2 Results of cox proportional hazard analysis displaying risk factors found to independently increase the risk of post-operative capsulotomy

Variable	Uni-variable		Multi-variable	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Decade of age[1]	0.68 (0.53-0.86)	0.003	0.74 (0.61-0.90)	0.007
Surgeon				
PGY3/PGY2	2.83 (1.63-4.9)	< 0.0005	2.39 (1.40-4.09)	0.002
PGY5/PGY2	6.03 (2.96-12.3)	< 0.0005	4.32 (1.89-9.87)	0.001
Sulcus lens, yes/no	3.43 (1.9-6.16)	< 0.0005	2.57 (1.32-4.99)	0.005
Ocular trauma, yes/no	2.84 (1.41-5.72)	0.003	2.34 (1.13-4.83)	0.020

[1]Younger patients are more likely to undergo YAG capsulotomy than older patients.

of sharped edged IOL optics over round edged optics placed into the capsular bag with regards to capsulotomy rates.

In addition to younger age, sulcus placement, clinical signs of ocular trauma and increasing surgeon experience were independent risk factors for capsulotomy. We found a 3% increase in the probability of capsulotomy with a one year difference in age. This translates into a 34% increased risk for PCO with a 10 years difference in age. The greater proliferation rate of equatorial lens epithelial cells in younger individuals is believed to be responsible for increased rate of PCO[10].

Patients in our study who had IOL placement into the ciliary sulcus were also at higher risk of capsulotomy. Sulcus IOLs have previously been reported to increase the risk of visually significant PCO[11,12]. A post-mortem prospective study of 3493 eyes found that fixation of the IOL outside the capsular bag was a significant risk factor for capsulotomy or central PCO in the visual axis[12]. When neither haptic nor IOL optic is placed inside the capsular bag, the IOL does not form an effective barrier to lens fiber migration and PCO ensues in the visual axis[12-14].

The increased probability of capsulotomy with increasing surgeon experience level stands in contrast to Elgohary[6] were no difference in capsolotomy rates were found by surgeon experience. Our observation may be partially explained by a referral bias at our institution where more experienced surgeons are referred more complex cases including those with poor mydriasis, pseudoexfoliation, evidence of ocular trauma, prior retinal or glaucoma surgery, extreme axial length, prior intravitreal injection, and mature cataracts even though none of these factors reached statistical significance as an independent risk factor for capsulotomy. While patients with ocular comorbidities may undergo more frequent follow up beyond routine annual exams and PCO may be detected and treated earlier, frequent follow up in diabetic patients did not result in a higher incidence of PCO compared to non-diabetics (15.3% *vs* 21.2% at 3 year)[6]. On the other hand, our data may be biased in that an unknown number of patients may have sought evaluation and treatment for PCO outside of the VA system locally or at a different VA eye care facility.

Furthermore, the use of capsulotomy as opposed to PCO formation as a primary endpoint and the reliance on multiple observers to diagnose the PCO may limit our findings. The probability of capsulotomy has been shown to increase steadily until it levels off at five year after phacoemulsification[4,9]. Further follow up will be required to assess whether this trend holds in our population.

Despite its limitations, this study demonstrates that the cumulative incidence of capsulotomy is significantly lower than previously reported in this teaching institution. However, PCO remains a common late sequelae of modern cataract surgery. The identification of patients at greater risk of capsulotomy, such as younger patients or those at risk for sulcus-placed IOL will allow for more thorough pre-operative disclosure, appropriate follow-up care, and enhance patient satisfaction.

COMMENTS

Background

This study sets out to evaluate the influence of surgeon experience on posterior capsule opacification (PCO) incidence. Prior studies evaluating the influence of surgical experience on PCO did not further differentiate data by year of training. Along with modern intraocular lens (IOL) design and evolution in surgical technique, from extracapsular cataract extraction to small incision phacoemulsification, capsulotomy rates have declined. While it is encouraging that the incidence of capsulotomy appears to be decreasing the reported rates in the literature cannot be extrapolated to a patient population at a teaching institution.

Research frontiers

The increased probability of capsulotomy with increasing surgeon experience level stands in contrast to prior observations. Patient referral based on case complexity may have introduced a selection bias.

Innovations and breakthroughs

Compared to prior studies, capsulotomy rates are in decline. This is attributable to new intraocular lens design and materials, advancements in surgical technique. In this study surgeon experience appeared to be associated with higher risk for capsulotomy. However this is likely due to selection bias, as more complex cases associated with greater risk of complications were referred to more experienced surgeons.

Applications

The identification of patients at greater risk of capsulotomy, such as younger patients or those at risk for sulcus-placed IOL will allow for more thorough pre-operative disclosure, appropriate follow-up care, and enhance patient satisfaction.

Peer review

This is a nice and well presented manuscript of posterior capsular opacification cumulative risk.

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RETROSPECTIVE STUDY

Considerations in the management of single-piece intraocular lenses outside the capsular bag

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Abstract

AIM: To investigate the outcomes of off label single-piece acrylic intraocular lenses (SPA-IOL) ciliary sulcus placement compared to three-piece IOL (3P-IOL).

METHODS: The charts of eight consecutive eyes of patients who received sulcus-placed SPA-IOLs between 2006 and 2009 were reviewed. None of the patients underwent IOL exchange. Charts of six age-matched patients who received sulcus placed 3P-IOLs were reviewed as a control group.

RESULTS: Mean follow up was 16 mo for SPA-IOL and 23 mo for 3P-IOL. Five of 8 patients in the SPA-IOL group required chronic use of IOP lowering medications at final follow up. Of these, one patient needed glaucoma implant surgery for uncontrolled IOP. One patient in the 3P-IOL group used chronic aqueous suppression pre- and postoperatively. Four of eight eyes with SPA-IOL were treated with chronic topical steroids and or non-steroidal anti-inflammatory drugs for cystoid macula edema, chronic uveitis, pigment dispersion syndrome or a combination of the above, compared to none in the control group. Mean best-corrected visual acuity was 20/35 in the SPA-IOL group and 20/47 in the 3P-IOL group.

CONCLUSION: Sulcus placed SPA-IOLs are associated with increased ocular morbidity. In select cases good visual acuity may be achieved. Due to postoperative rotation of sulcus placed toric SPA-IOLs stable astigmatism correction cannot be achieved. Alternative intraocular lenses should be considered when in-the-bag placement of SPA-IOL is not possible.

Key words: Cataract surgery; Sulcus intraocular lens implant; Single piece intraocular lenses; Three piece intraocular lenses; Posterior capsule tear; Cataract surgery complication; Pigment dispersion; Cystoid macula edema; Posterior capsule tear; Anterior vitrectomy

Core tip: Single-piece acrylic intraocular lenses implants are FDA approved for placement into the capsular bag. Their off label placement into the ciliary sulcus is not recommended by the manufacturer and has been the subject of controversy in ophthalmology. This retrospective case series is unique in that patients were followed for 16 mo (range 1.2-37 mo) without intervention and visual outcomes and comorbidities were evaluated and compared with eyes receiving standard of care sulcus placed three-piece intraocular lenses implants.

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Table 1 Patient demographics

	Case (*n*)	Age at surgery	Operative eye	IOL implanted	Pre-op glaucoma diagnosis
SPA-IOL group	1	80	OD	SN60WF	No
	2	85	OD	SN60WF	No
	3	87	OS	SN60T5	No
	4	76	OD	SN60WF	No
	5	71	OS	SN60WF	No
	6	79	OS	SN60T5	No
	7	87	OD	SN60WF	Suspect
	8	76	OD	SN60WF	No
Three-piece IOL group	9	86	OD	MA60AC	Suspect
	10	74	OD	MA60AC	No
	11	88	OD	MA60AC	No
	12	86	OS	MA60AC	No
	13	76	OS	MA60AC	No
	14	87	OS	MA60AC	Yes

SPA-IOL: Single-piece acrylic intraocular lenses.

INTRODUCTION

With the advent of small incision cataract surgery, and the development of premium intraocular lenses foldable single-piece acrylic (SPA) intraocular lenses (IOLs) have gained in popularity. For example, over 50 million AcrySof® (Alcon, Ft. Worth, Texas) IOLs have been implanted world- wide[1]. The SPA-IOL has been modified to allow for concomitant astigmatism (toric IOL) and presbyopia correction (multifocal IOL) at the time of cataract surgery. The SPA-IOL design assures excellent apposition with the posterior capsule allowing stability within the capsular bag. When placed in the bag the SPA-IOL allowed for more posterior position relative to the iris than a 3P-IOL[2]. Excellent biocompatibility and design reduce the incidence of posterior capsule opacification (PCO)[3,4]. Due to zero angulation of the haptic-optic junction it is not recommended to place SPA-IOLs into the ciliary sulcus[5].

Chang *et al*[6] reported a series of 30 patients in a referral setting with complications related to sulcus placed SPA-IOLs. The authors strongly suggest IOL exchange as primary treatment and review alternative IOL choices for primary cataract surgeons. Conversely, Taskapili *et al*[7] reports on 89 eyes with sulcus placed SPA-IOL compared with 72 eyes with sulcus placed PMMA IOL and suggesting equal, low rates of complications, glaucoma 19% *vs* 16%, CME 8% *vs* 17%, anterior uveitis 6% *vs* 7%, IOL decentration 4% in both. Endophthalmitis was observed in the control group only (2 of 72 eyes). Other known complications associated with sulcus placed SPA-IOL include pigment dispersion syndrome, iris chafing, uveitis-glaucoma-hyphema syndrome and vitreous hemorrhage[8-12]. Uy *et al*[13] noted 35% incidence of pigment dispersion and secondary glaucoma in 15% of 20 patients with sulcus placed SPA-IOL.

The cases presented here are unique because they constitute a consecutive case series of eyes with posterior capsular tear, anterior vitrectomy, and off-label placed SPA-IOLs compared with three-piece IOLs in the ciliary sulcus at a single hospital. Within this institution, one surgeon routinely placed SPA-IOLs in the ciliary sulcus if there was capsular support, and other surgeons did not. Given the controversy, we aimed to review cases of sulcus placed SPA-IOLs to determine visual outcomes and complications. No cases were referred from outside centers, and all operative and perioperative data was well documented in the electronic medical record.

MATERIALS AND METHODS

This is a retrospective chart review of fourteen consecutive patients who underwent cataract surgery complicated by posterior capsule tear and sulcus placed IOL at one medical center. The study was approved by the institutional human subjects review board. Eight eyes with sulcus placed SPA-IOLs and six eyes with three-piece (3P) acrylic IOLs were included. One patient was lost to follow up after one month. All patients were male, mean age was 80 years (range 71-87 years) at the time of surgery. Demographic characteristics of the two groups were similar and are summarized in Table 1. During phacoemulsification a posterior capsule tear with vitreous prolapse was encountered. Anterior vitrectomy was performed and the IOL was placed into the ciliary sulcus. None of the eyes had retained lens material at the end of the procedure. Six of the SPA-IOLs were monofocal Acrysof® SN60WF implants, two implants were toric SPA-IOLs. No IOL was suture fixated to the iris or the sclera.

RESULTS

Clinical data on all patients in the two IOL groups are summarized in Table 2. Mean pre-operative spherical equivalent was similar in the SPA-IOL and 3P-IOL groups (+0.47 and +0.32 respectively). Persistent iritis, pigment dispersion and CME were documented in several patients with SPA-IOL, while only one patient with a 3P- IOL had documented CME after surgery. No patient with 3P-IOL had pigment dispersion or prolonged iritis defined as anterior chamber cellular reaction present more than one month after surgery. It is also noteworthy that in the SPA-IOL group, elevated intraocular pressure above 21 mmHg was recorded in 63% of cases. This was treated with intraocular pressure lowering medications beyond postoperative week one. One of the eyes had aqueous drainage implant surgery. The patients were continued on glaucoma medications six month or more after surgery. In contrast, only patient in the three-piece IOL group required intraocular pressure lowering medication after post operative week one, this patient had pre-existing glaucoma. Best corrected visual acuity (BCVA) was 20/30 or better in 4/8 patients in the SPA-IOL group and in 3/7 patients in the 3P-IOL group at post-op month one. In the 3P-IOL group poor vision at month one was attributable to suture-induced astigmatism and resolved after suture removal. Four of eight patients with SPA-IOL and four of six with 3P-IOL achieved a BCVA of 20/30 or better at the time of last follow up.

Table 2 Pre- and postoperative best corrected visual acuity

	Case	Pre-op BCVA	Pre-op refraction	POM1 refraction	POM1 BCVA	Most recent BCVA	Re-operation	CME	PDS	Post-op Glc meds	Glc meds last F/U	Months of F/U
SPA-IOL	1	20/50	+1.25 + 1.25X012	-4.50 + 4.75X001[1]	20/40	20/20	Wound leak	No	No	Yes	No	37
	2	20/60	-3.25 + 3.50X180	-2.75 + 2.25X003	20/50	20/50	Bgi	Yes	No	Yes	No	32
	3	20/100	+0.50 + 0.50X180	-3.75 + 3.00X138	20/20	20/40	No	No	Yes	No	No	7
	4	20/60	-0.75 + 1.00X163	-1.50 + 1.75X005[1]	20/25	20/25	No	No	No	No	No	15
	5	20/70	+3.25 + 1.00X105	+2.00 + 0.75X105[1]	20/60	20/50	No	Yes	Yes	No	No	19
	6	20/40	+0.50 +2.25X178	-3.75 + 3.75X025[1]	20/40	20/40	No	Yes	Yes	Yes	Yes	15
	7	20/60	-3.25 sph	-2.75 + 2.00X015	20/25	20/25	No	No	No	Yes	Yes	1.5
	8	20/40	+0.75 sph	-0.50 + 1.00X125	20/30	20/30	No	No	No	Yes	Yes	1.2
Three-piece	9	20/60	-5.75 + 2.00X177	-2.00 + 1.75X175	20/30	20/30	No	Yes	No	No	No	31
IOL	10	20/80	-2.50 + 0.50X155	Unable[1]	20/400	20/60	No	No	No	No	No	38
	11	20/60	+3	-1.75 + 1.75X004[1]	20/25	20/25	No	No	No	No	No	2
	12	20/70	+2.00 + 1.25X162	Unable[1]	CF	CF[2]	No	No	No	No	No	25
	13	20/50	-2.00 + 2.25X005	-2.50 + 1.00X0061	20/60	20/25	No	No	No	No	No	2
	14	20/100	-2.75 + 1.50X165	Unable[1]	CF	CF[3]	No	No	No	Yes	Yes	24

[1]Patients 10, 12, and 14 were not able to achieve a refraction at the post-operative month 1 visit. In all cases, this was attributed to sutures present at the clear corneal incisions; [2]Patient 12 achieved a visual acuity of 20/40 at post operative month 7 (-2.50 + 3.75X168) and later lost vision (Count Fingers) attributed to wet age related macular degeneration; [3]Patient 14 achieved a visual acuity of 20/50 at post operative month 2 (-2.75 + 3.00X165) and later lost vision (Count Fingers) due to advanced glaucoma. PDS: Pigment dispersion syndrome; SPA-IOL: Single-piece acrylic intraocular lenses.

Two patients in the 3P-IOL group had documented comorbidities preoperatively and therefore reduced visual prognosis. One eye was diagnosed with age related macula degeneration (ARMD) and one eye with advanced glaucoma. Loss of follow up after two month or less occurred in two individuals (25%) with SPA-IOL (one patient deceased, one for unknown reason) compared to three patients (43%) in the 3P-IOL group (for unknown reasons). All patients lost to follow up had best corrected visual acuities of 20/30 or better at their last exam.

DISCUSSION

The question of whether SPA-OLs should be placed in the ciliary sulcus is not decisively answered in the peer reviewed literature. Many previous reports have been case reports[7,8,12-17], or are comprised of patients referred to tertiary care centers for management of complications[6,11,18-20]. This case series shows that good corrected visual acuity can be achieved with sulcus placed IOLs of either SPA or three-piece type, however, visual recovery was prolonged in several cases using both types of IOL. Secondary intervention was needed in 20% of cases (two of eight eyes) after SPA-IOL. Importantly, this case series is not based on referral to a tertiary care center for complications associated with the procedure and may therefore represent an unbiased look at a controversial issue.

We believe that SPA-IOL rotation, even months after implantation, did occur in some patients and resulted in unstable manifest refraction in at least one patient who had received an AcrySof® toric SN60T5 lens (Alcon, Ft. Worth, Tx). The AcrySof® SPA-IOL has a diameter of 13 mm from end to end and is thus shorter than the ciliary sulcus diameter of most eyes. There is no accurate way to estimate the ciliary sulcus diameter by external measurements. In addition, the horizontal sulcus diameter is typically shorter than the vertical diameter[21]. Therefore, an initially well centered SPA-IOL in the sulcus may later decenter following rotation into a wider sulcus meridian, unless reverse optic capture can be achieved[22]. SPA-IOL decentration after initial correct placement is particularly undesirable in patients with high visual expectations after premium (toric or multifocal) IOL implantation. Given the possibility of rotation after sulcus implantation of toric SPA IOL, it appears preferable to instead implant an alternate three-piece lens combined with other methods of astigmatism correction such as limbal relaxing incisions. Suture fixation of SPA IOL has been reported to result in stable lens position in the literature but was not attempted our cases.

Placement of any posterior chamber IOL in the ciliary sulcus carries increased risk for complications such as pigment dispersion due to IOL proximity to the iris[23]. A three-piece posterior chamber IOL with posterior angulation of the haptics will move the optic away from the posterior pigment epithelium of the iris. Additionally, a three-piece IOL with a relatively thin optic edge and small, round haptics will reduce potential problems related to iris chafing when placed in the sulcus. The full picture of uveitis-glaucoma-hyphema syndrome was not observed in our case series, though pigment dispersion and iris transillumination defects were noted in three of eight patients with SPA-IOLs and in none of the eyes with 3P-IOLs. Perhaps more importantly, chronic secondary glaucoma developed in several patients with SPA-IOL, although it is unclear whether this was a direct result of pigment dispersion alone. None of the patients in this series underwent IOL exchange as of their most recent follow-up. It should be noted that this study includes a relatively small number of patients and is retrospective in nature. As such, it may lack sufficient power to definitively demonstrate differences between the two IOLs implanted in the cilliary sulcus.

A recent report on complications after SPA-IOL im-

plantation into the sulcus[6] and the corresponding editorial[24] provide a comprehensive review and discussion of associated risks, complications, and management of complications. Surgical alternatives for SPA-IOL placement in the sulcus are detailed and discussed in that publication. Technological advancement in cataract surgery has raised today's patients' and surgeons' expectations for an elegant, fast surgery followed by a smooth postoperative course and rapid visual recovery. While posterior capsular rupture inherently leads to a more complex surgery, our results suggest that a three-piece IOL in the sulcus is preferred over an SPA-IOL in such situations. New developments in IOL design may allow reliable use of SPA-IOL in the sulcus[25].

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COMMENTS

Background

Single-piece acrylic intraocular lenses (SPA-IOL) implants are FDA approved for in the bag placement. There is controversy about the SPA-IOL placement in the ciliary sulcus when in the bag placement is not feasible. Surgeons at tertiary centers advocate categorical IOL exchange to achieve stable IOL position and eliminate IOL induced complications such as iris chaffing, uveitis-glaucoma-hyphema syndrome, fluctuating visual acuity, glaucoma and others.

Research frontiers

The clinical course after sulcus placed SPA-IOL is not known. The experience with sulcus placed SPA-IOL at tertiary care centers is hampered by selection bias due to referral of more complicated cases. This retrospective case series offers an unbiased evaluation of sulcus placed SPA-IOLs compared to the alternative three-piece IOL (3P-IOL) placement.

Innovations and breakthroughs

With the introduction of small incision phacoemulsification and premium IOLs not necessitating wound enlargement for IOL inserting, the temptation exists to use a SPA-IOL in the sulcus. This off label use does not achieve as stable a placement as when positioned in the capsular bag. Postoperative prevalence of cystoid macula edema, pigment dispersion, and need for glaucoma medications is increased after sulcus placed SPA-IOL compared to 3PA-IOL. IOL exchange can be deferred on a case by case basis.

Applications

This retrospective study illustrates the sequelae of SPA-IOL placement in the sulcus and clinical results in eyes were IOL exchange was not pursued.

Terminology

The terminology used here should be familiar to any eye care specialist.

Peer review

This paper is interesting and can be accepted.

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

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14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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