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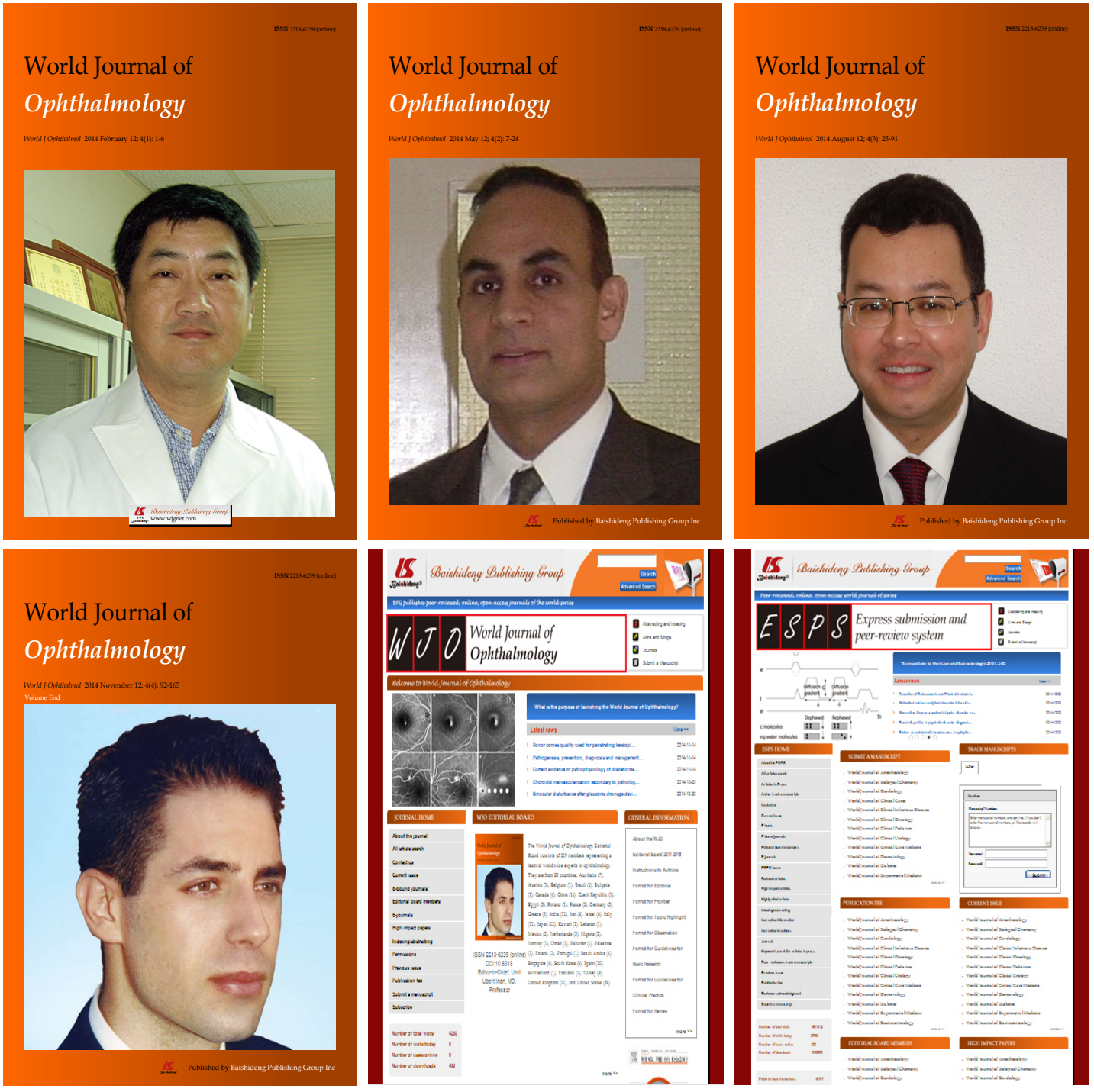

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MINIREVIEWS

Ocular damage secondary to lights and lasers: How to avoid and treat if necessary

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Abstract

An armamentarium of the latest light and laser technologies are used by physicians of different disciplines to address a variety of aesthetic challenges in the periocular region and throughout the body. If improperly used, these modalities can inflict serious ocular injury on the patient, support personnel, and operator. It is paramount that providers involved in operating these technologies be knowledgeable about the physical and clinically relevant properties of the unit being used. This involves training in the proper utilization, appropriate treatment parameters, and safety measure for each. Selection of the appropriate eye protection is particularly important for both the patient and the personnel. It is also imperative for the laser operator to understand the range of potential ocular complications associated with the cosmetic use of lasers and lights, to recognize the signs and symptoms associated with ocular damage, and to provide efficient first aid measures should damage ensue. Possible ocular complications related to the cosmetic use of lasers and lights range from mild eyelid swelling and erythema to potentially blinding macular injury. Ocular injury may also be inflicted by the improper selection or placement of eye protection. A complete ophthalmologic evaluation and timely management of potential complications is mandated when there is any concern for ocular injury.

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Key words: Laser; Intense pulsed light; Cosmetic; Laser safety eyewear; Ocular complications; Aesthetic

Core tip: The selection of the appropriate laser safety eyewear (LSE) and eye shields while performing laser and/or light therapy to the face and periocular region may, among other precautionary measures, prevent the occurrence of ocular complications that can sometimes be severe and even blinding. Since LSE is specific for each particular wavelength, extreme caution should be exercised to avoid selecting the inappropriate LSE. The choice of external or corneal shields for the protection of the patient's eyes depends on the particular area to be treated.

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INTRODUCTION

Light rays, whether naturally occurring (solar) or medically used, have a range of effects on the eye and the surrounding tissues depending on the wavelength of light, the nature of exposure, and whether protective mechanisms are applied. Lights can be classified according to their wavelength on the electromagnetic spectrum into ultraviolet rays (UVR; wavelength 100-400 nm), visible light (400-700 nm), infrared (700-1200 nm) and far

Table 1 Classification of laser systems

Class 1	Considered to be incapable of producing damaging radiation levels during operation and are safe under all conditions of normal use to naked eye or magnifying optics. These systems are exempt from any control measures or other forms of surveillance. Examples are lasers used in diagnostics in laboratories
Class 1M	Considered to be incapable of producing hazardous exposure conditions during normal operation unless the beam is viewed with an optical instrument (magnifying optics)
Class 2	Low power laser systems; they emit in the visible portion of the spectrum (400-700 nm), and are considered safe because aversive mechanisms (*i.e.*, the blink reflex) afford protection. An example is the helium-neon laser (laser pointer)
Class 2M	Emit in the visible portion of the spectrum. Eye protection is normal afforded by the aversion response for unaided viewing. However, these systems are potentially hazardous when viewed with certain optical aids
Class 3	Medium power laser systems; they may be hazardous under direct and specular reflection viewing conditions. They are normally not a diffuse reflection or fire hazard. An example of a class 3 laser is the Nd:YAG laser used in ophthalmology. There are 2 subclasses: 3R and 3B
Class 3R	Can be hazardous under some direct and specular reflection viewing condition if the eye is appropriately focused and stable, but the probability of an actual injury is small. They will not pose either a fire-hazard or diffuse-reflection hazard. They are safe if handled carefully with restricted beam viewing
Class 3B	May be hazardous under direct and specular reflection viewing conditions, but are normally not a diffuse reflection or fire hazard
Class 4	High power systems and are the most dangerous. They are hazardous to the eye or skin from the direct beam, may pose a diffuse reflection or fire hazard, and may produce laser-generated air contaminants and hazardous plasma radiations. Examples include the CO_2, argon, continuous wave Nd:YAG, and pulsed dye laser

infrared (> 1200 nm). UVR can be further subdivided to UV-A (315-400 nm), UV-B (280-315 nm) and UV-C (100-280)[1]. Only UV-A and a small portion (10%) of UV-B reach the earth surface and therefore have an opportunity for ocular exposure.

Laser radiation wavelengths fall within the ultraviolet, visible and infrared wavebands of the electromagnetic spectrum. The shorter, biologically active wavelengths (below 300 nm) are mostly absorbed at the cornea, while the longer wavelengths pass through the cornea to reach the lens and retina[1]. Lights and lasers with wavelengths from 400 nm to 1400 nm (retinal hazard region) are particularly dangerous as they can be transmitted through the clear media of the eye and become focused on the retina. While a portion of the retinal hazard zone falls within the visible light spectrum (400-700 nm), which will trigger the blink reflex and protect the eye, the invisible portion falling in the 700-1400 nm waveband constitutes a major window of danger.

UVR

The main source of UVR that the eye and periocular tissues are exposed to is sunlight. A range of conditions involving the eyelids, the ocular surface, the crystalline lens, the retina and choroid have been strongly linked to acute or cumulative UVR exposure[1]. Detailed discussion of UVR effects on the eye and protection from solar radiation is beyond the scope of this article.

LASERS AND INTENSE PULSED LIGHT

Laser properties such as coherence and low divergence, together with the focusing mechanism of the eye optical system, can result in significant ocular injury if specific safety measures are not strictly followed. This can be particularly devastating if the retina is the recipient of end-organ damage. Because of the sensitivity and vulnerability of the eye to overstimulation, laser safety guidelines are largely established on injury thresholds of the ocular structures, especially the retina[2]. Furthermore, lasers are classified according to the ability of the laser beam to cause biological damage to the eye or skin during use (Table 1)[3,4].

Absorption and scattering are important concepts in understanding tissue response to laser and light exposure[4]. Absorption depends on the tissue's affinity for the laser's wavelength. Specific wavelengths are preferentially absorbed by a specific tissue chromophore which has a different absorption spectrum determined by its chemical structure. The most clinically relevant organic chromophores are water, hemoglobin and melanin. For example, to treat a vascular lesion, oxyhemoglobin, the predominant form of hemoglobin, is chosen as a target chromophore. It has absorption peaks of 418 nm, 542 nm, and 577 nm.

Scattering is also related to wavelength. Shorter wavelength lasers (cold lasers; below visible spectrum; *e.g.*, Excimer laser) have a greater scatter and less tissue penetration, while the reverse is true for longer wavelength lasers[4]. The action of lasers also depends on the power (watts/s; joules/s), the spot size (cm^2) and the duration of action. With larger spot size, there is less scattering but deeper tissue penetration.

Although lasers target specific chromophores, the surrounding scatter and the resulting thermal effect can cause collateral damage[4]. Thermal damage occurs when enough energy is absorbed by a suitable chromphore at a faster rate than the resultant heat can be dissipated[5,6]. Also, while the main tissue chromophores are targeted, other ocular structures that are also rich in these chromophores are susceptible to inadvertent damage (*e.g.*, retina rich in hemoglobin and melanin; uvea rich in melanin; cornea and lens rich in water).

Mechanisms of laser injuries to the eye vary according to the type of laser used and the properties of the particular ocular structures. Lasers and lights in the retinal hazard region (wavelength 400-1400 nm) can cause significant injury to the macula due to the focusing ability of the crystalline lens. For example, argon laser (wave-

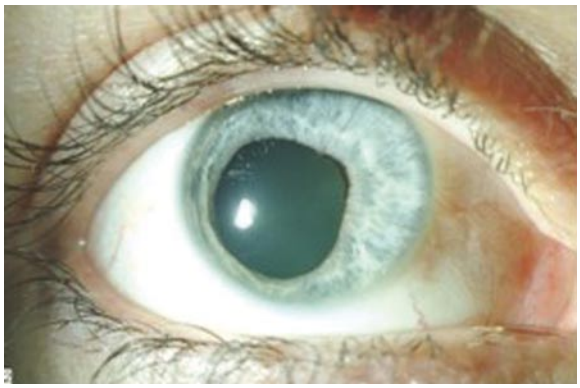

Figure 1 Anterior view of the right eye of a patient with pharmacologic pupillary dilation showing iris atrophy and pupillary distortion secondary to posterior synechia following inadvertent ocular intense pulsed light injury.

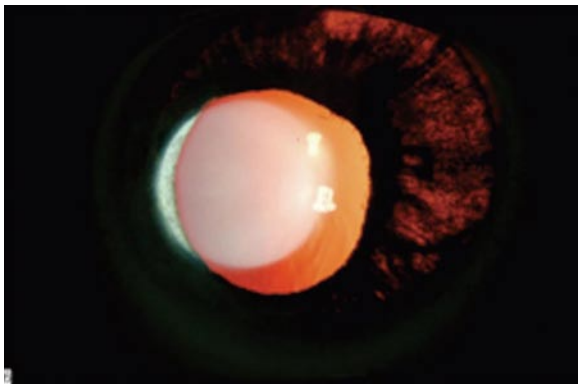

Figure 2 Slit lamp photograph of the right eye of the patient in Figure 1 showing iris transillumination defects.

length 488 nm and 515 nm) is mainly absorbed by vessels and melanin. If improper eye protection is used, the laser can pass through the cornea, become focused by the lens onto the retina, and result in heat denaturation of proteins (photocoagulation)[4,7].

Lasers in the near- and mid-infrared spectrum (*e.g.*, Nd:YAG, wavelength 1064 nm, used for various indications such as vascular lesions, hair removal and rejuvenation) have longer wavelengths and are weakly attracted to melanin, relative to other lasers, with subsequently less melanin chromophore absorption[8], but can still cause retinal damage[4,9]. It should be emphasized that lasers in the 700-1400 nm band of the spectrum are particularly hazardous because while they are invisible to the eye, they can still cause serious ocular injury.

Although lasers in the far infrared spectrum (wavelength 1400-10600 nm) cannot penetrate the ocular tissues far enough to reach the retina, these wavelengths can still cause injury to the cornea and crystalline lens. Carbon dioxide (CO_2) laser (wavelength 10600 nm) is an ablative laser used to achieve skin tightening and for the treatment of certain vascular lesions such as orbital lymphangioma[7]. Its main target chromophore is intracellular water, which is instantaneously vaporized with application of the laser, resulting in lateral thermal damage and coagulative necrosis of the surrounding tissues. The CO_2 laser can cause corneal or scleral injury due to their rich water content[4,7].

Erbium:YAG laser (wavelength 2940 nm), another ablative laser, which can also be used in a fractional manner, is more efficiently absorbed by water and collagen, inducing less thermal damage than CO_2 laser. Complications of these lasers include erythema, hyper- and hypopigmentation, skin infections, and accidental corneal injury.

Intense pulsed light (IPL) is a non-ablative technology used to treat telangiectatic lesions, skin pigmentation and abnormal skin texture[10]. The device emits non-collimated, non-coherent lights of multiple wavelengths (500-1200 nm; within the retinal hazard zone). Although it is, therefore, not classified as a laser, this modality can still cause significant ocular damage. Pigmented structures, like the iris, are extremely susceptible to accidental injury during IPL treatment. The senior author (WL) published a retrospective review of two cases with permanent ocular damage secondary to IPL performed at outlying facilities and referred for management of complications[10]. Both patients developed severe eye pain, anterior uveitis, pupillary distortion (Figure 1), permanent iris atrophy (Figure 2) and photophobia. There tends to be a false sense of security when dealing with light therapy because many operators do not realize the potential damage that this technology can cause to the eye. Most damage occurs when operators either reposition the eye shields to treat awkward areas such as the medial canthus, or they don't use eye protection at all. It is important to know the dangers of light therapy as well as laser therapy.

There are numerous reports of inadvertent laser ocular injuries in the literature. Park *et al*[11] reported a case of a patient who sustained macular injury following accidental exposure to Q-switched Nd:YAG laser (1064 nm). The patient experienced instantaneous bright flash light perception followed by loss of vision (best corrected visual acuity 20/100 in affected eye immediately following exposure). Examination revealed metamorphopsia and central scotoma by Amsler grid, and a laser macular burn and vitreous hemorrhage by fundoscopy. Despite treatment with oral prednisolone (60 mg daily with a 10 mg/wk taper), the patient developed an epiretinal membrane that spontaneously regressed later and visual acuity remained 20/100. At six-year follow up, the patient's visual acuity had not improved and fundus exam revealed a centrally pigmented chorioretinal scar in the macula.

Marcus *et al*[12] reported another case of a laser ocular injury where the patient was exposed to YAG laser without safety goggles when the triggering mechanism of the laser accidentally went off. The patient noticed immediate loss of vision and a black spot in the center of her vision. She could only count fingers one hour after exposure. Fundus examination revealed a mild vitreous hemorrhage near the fovea, and fluorescein angiography showed two choroidal ruptures at right angles to each other through the center of the fovea. A full thickness macular hole developed a week later, and subretinal neovascularization

was identified alongside the superior edge of the macular hole six months later, with a subsequent metaplastic scar formation and enlargement of the macular hole. The visual acuity stabilized at 20/200 in the affected eye as documented in a nine-year follow up. Surgical treatment of the patient was not attempted.

Sun *et al*[13] reported a case of an early subfoveal choroidal neovascular membrane (CNV) in a technician who accidentally looked into the path of a 532 nm pulsed green light beam. The patient experienced an immediate flash of bright pink light followed by an immovable shadow in the central vision four hours later. Examination only five days following exposure revealed a best corrected visual acuity of 0.08 (decimal) and a small subfoveal grayish-yellow lesion on fundoscopy representing a CNV. Fundus fluorescein angiography showed a lacy hyperfluorescent pattern with subsequent leakage. The patient received no treatment on the ground of cost and on four-month follow up her best corrected visual acuity was found to have improved to 0.01 (decimal) while the lesion was unchanged in appearance by fundoscopy.

Harris *et al*[6] described ten cases of laser ocular injury that occurred in the United States military between 1984 and 2000. Most of the cases were caused by accidental exposure to Q-switched Nd:YAG laser (1064 nm). Eye protection was not worn by any of the victims at the time of injury. Injuries described included vitreous hemorrhage, preretinal hemorrhage, macular hemorrhage, subretinal hemorrhage, vitreous detachment, parafoveal scarring, progressive macular scarring, macular pucker, retinal burns, macular/retinal edema, retinal pigment epithelial disruption, macular hole, epiretinal traction membranes, central serous retinopathy and punctate macular lesions.

PREVENTION OF OCULAR DAMAGE

Eye protection during cosmetic procedures with lights and lasers during treatment administration is of paramount importance for the patient, the operator, the observer and the assistant[14]. With the advent of new laser devices operating at multiple wavelengths, understanding the hazards of lasers and lights has become even more critical. Despite the increased knowledge of lasers and laser safety, eye injuries in the workplace still occur, even with the use of protective eyewear.

General protective measures that guard against accidental laser injuries include warning signage and proper personnel training. Laser warning signs must be placed at the entrance of the laser treatment room when lasers are operating. Adequate laser safety training for personnel must be provided. Extra care should be taken when the laser is taken off "standby" mode, as lasers can be initiated by accidental pressing of the foot switch while the hand-piece is directed away from the patient or toward their unprotected eye[14].

Potential injury to the eyelids can be minimized by adjusting the treatment parameters appropriately, using cooling devices during the procedure, applying ice packs after the procedure, and elevating the head of the bed. Patients should be informed of what to expect pre- and post-treatment, like edema and erythema. Potential ocular complications can be avoided or minimized by means of careful application of topical anesthetics, proper sizing, sterilization and gentle placements of corneal shields. Excessive pressure on the globe during treatment should be avoided. Corneal shields should be removed carefully, and the lids cleansed appropriately post-treatment.

Early recognition of ocular complications is critical. Symptoms and signs of eyelid complications include erythema, edema, pain, burning, abnormal sensation of lids and pinpoint bleeding. Laser damage to the eye itself may go unrecognized initially. It can be painless, or the operator might hear a "pop" sound. Patients might complain of photophobia, redness, tearing or blurry vision following the procedure, Other clinical signs include pupil abnormalities or a new blind spot in the patient's vision. Subconjunctival hemorrhage, infection, chemical irritation and corneal abrasion can occur as a result of laser and/or protective eyewear injury. All of these signs and symptoms can represent serious, sight-threatening laser or light injuries to the cornea, sclera, iris, or retina. If the clinician is suspicious of an injury, a full, thorough ophthalmologic evaluation must be performed in a timely manner.

LSE FOR THE STAFF

Choosing the appropriate eye protection for everyone in the treatment room is the key to prevention of ocular damage. The American National Standards Institute has established guidelines for laser safety and defines maximum permissible exposure (MPE) levels, which is the amount of laser radiation exposure allowable without hazardous effects for specific laser wavelengths[3].

Each laser requires a specific type of eyewear depending on its specific wavelength and peak irradiance[12]. Optical density (OD) of the LSE determines its ability to reduce the energy of a specific laser wavelength to a safe level (below MPE). The OD of a specific goggle should be engraved on the side of the eyewear (Figure 3). Occasionally, a drawing of the hand-piece is placed on the side of the goggle (Figure 4) to avoid confusion. OD is expressed as the logarithmic value of the incident beam irradiance divided by the transmitted beam irradiance. As such, an OD of 1.0 allows 0.1% of laser energy to be transmitted through the goggle lens, while an OD of 6 allows only 0.000001% of laser energy to be transmitted, virtually protecting the eye from direct beam exposure.

Another important factor to consider when choosing LSE is the visible light transmittance (VLT)[15]. LSE should be able to filter out the laser wavelength while transmitting as much light as possible so the operator can visualize the treatment area. The ideal LSE should have both a high OD and VLT for the particular wavelength of the laser used. The style, field of view and comfort of the LSE are also important as they can affect the compliance of personnel. Regarding IPL, the LSE able to protect in this entire range (400-1200 nm) would offer little

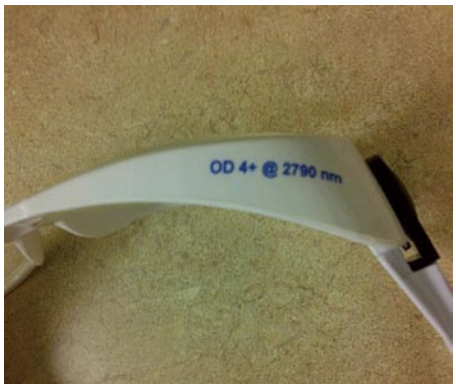

Figure 3 Optical density engraved on laser safety eyewear.

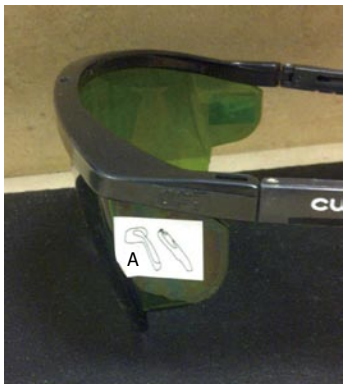

Figure 4 Drawing of the hand-held delivery system is placed on the side of the goggle.

Figure 5 Shutter glasses used for intense pulsed light.

visibility (low VLT). Goggles with a fast shutter mechanism that detects light intensity and immediately dims the filter can be utilized for IPL (Figure 5).

EYE PROTECTION FOR THE PATIENT

Eye protection for the patient depends on the area to be treated. If the crows' feet, face, or skin overlying the orbital rim are treated, external eye protection, made of either stainless steel (Figure 6A) or stick-on fabric (*e.g.*, Coverlet Eye Occlusor, BSN Medical Inc., NC) (Figure 6B), can be used. When using the adhesive eye patches, the skin should be cleansed and dried off. Patients should be asked about contact allergies, as the adhesive patches may contain latex.

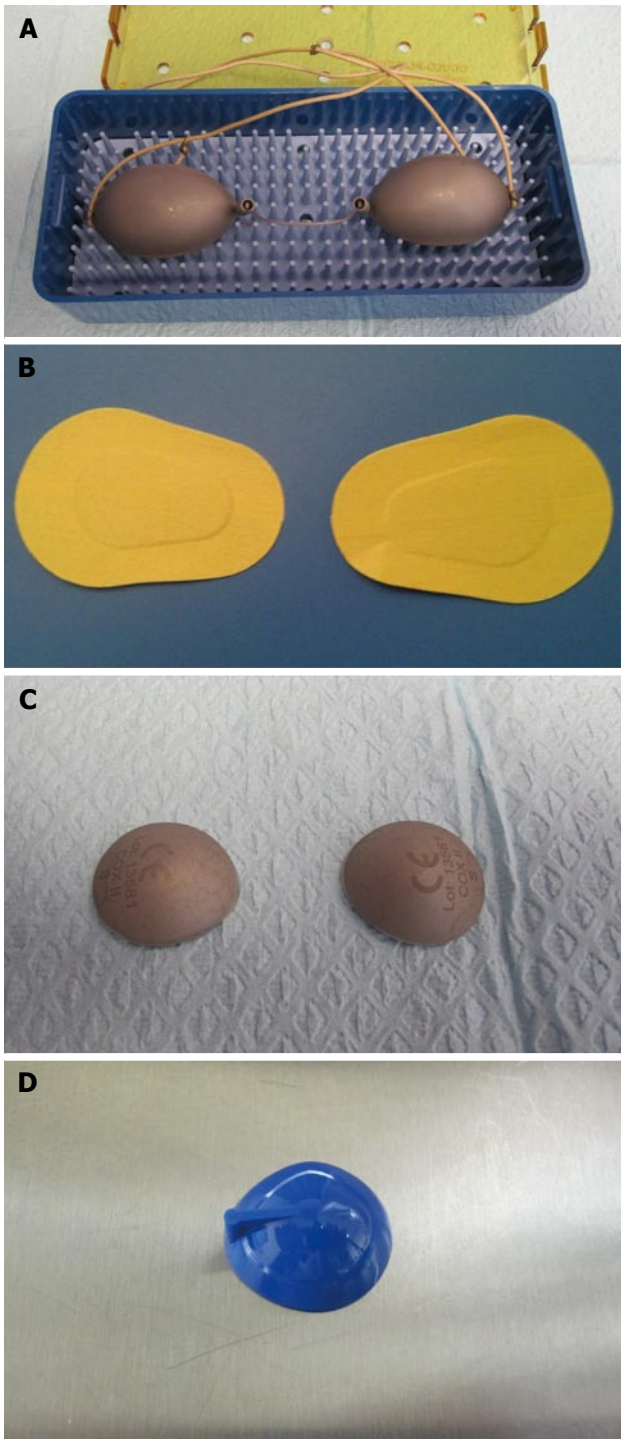

Figure 6 Shields. A: Stainless steel external shield; B: Stick-on fabric external eye shield; C: Stainless steel corneal shields; D: Methyl methacrylate corneal shields.

If the treatment is to be performed on the eyelid itself, corneal shields should be used. They allow treatment all the way up to the lash line. Furthermore, they provide a taut surface over which the laser hand piece can more easily glide.

Corneal shields, however, have the potential to induce corneal abrasions if extreme care is not taken. The operator should make sure that there are no contraindications

for corneal shield placement, such as recent ocular trauma or corneal surgery. Contact lenses should be removed and 1-2 topical anesthetic drops instilled before placing the corneal shield. Corneal shields should be checked for sharp edges and for debris prior to each use. Stainless steel corneal shields (Figure 6C) can be gas or steam autoclaved. They are buffed and electro-polished to a smooth surface, and are less likely to conduct heat. However, they can be more susceptible to the development of sharp edges. Methyl methacrylate corneal shields (Figure 6D) can be gas autoclaved. However, there is a risk of thermal conduction associated with their use if the laser beam comes in contact with the shields.

MANAGEMENT OF OCULAR COMPLICATIONS

All operators of lasers should be able to recognize ocular laser injury and be prepared to provide the necessary first-aid measures. It is important for ophthalmologists performing laser treatments to have an eye wash station, a slit lamp, fluorescein stain, dilating eye drops and lenses for possible fundoscopy. A copious, profuse irrigation with sterile eyewash solution should be performed if the patient complains of foreign-body sensation, irritation or pain. A thorough slit lamp evaluation with corneal fluorescein staining may be required. Blurry vision after eye shields are removed may also occur secondary to anesthetic, tears, or mucous on the surface of the eye, and is first treated with copious irrigation with saline or eyewash. If symptoms persist or if the patient complains of photophobia, blepharospasm or significant diminution of vision, a thorough slit lamp examination and fundoscopy should be performed. Appropriate referral to a subspecialist is warranted in the unfortunate event of a significant injury, particularly to the retina. Cases are then managed according to the type of injury inflicted. Unfortunately, many of the patients who sustain laser ocular injuries with macular involvement end up with permanent visual loss.

CONCLUSION

The role of lasers and lights has become increasingly popular in aesthetic medicine. Due to the physical properties of light, tissue-light interaction and human error, damage to ocular structures can occur if precautionary measures are not strictly followed. Proper training of personnel on laser and light properties, use and safety is key to preventing serious ocular and soft tissue complications in the patient as well as the personnel. Potential ocular injury can be minimized by adhering to a relatively simple set of safety measures, including the choice of appropriate protective eyewear and eye shields. If ocular injury is suspected, prompt ophthalmologic evaluation and treatment is mandatory.

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REVIEW

Ablative laser assisted topical delivery of antifibrotics in the management of cicatricial ectropion

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Abstract

A variety of surgical techniques have traditionally been used to manage cicatricial ectropion. These techniques primarily aim at vertical lengthening of the anterior lamella and include a variety of skin flaps and grafts. Alternative techniques such as dermal filler injection to support the eyelid margin may also be used in the management of select patients with cicatricial ectropion. The application of different types of laser for scar revision throughout the body has rapidly evolved; similar mechanisms, principles and treatment rationale can be applied to the use of lasers in the management of cicatricial ectropion. Additionally, ablative lasers, such as Carbon Dioxide and Erbium:yttrium-aluminum-garnet lasers, may be used in the transdermal delivery of antifibrotic agents, such as interferon gamma, interferon alpha, vitamin D, triamcinolone and 5-fluorouracil, resulting in efficient target tissue penetration, limitation of systemic drug toxicity and decreased degradation. Although the combination of ablative fractional resurfacing and topical antifibrotic agents is a new treatment modality, there is a great potential for its efficient utility in the management of periocular scarring and cicatricial ectropion. The introduction of these innovative therapeutic modalities offers ophthalmologists a greater range of possible effective treatments to address periocular scar tissue and the resultant cicatricial ectropion.

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Key words: Laser; Antifibrotic agents; Cicatricial ectropion; Periocular scarring; Ablative fractional resurfacing

Core tip: There is a broad range of conservative as well as more invasive treatment modalities for cicatricial ectropion. Ablative lasers can be used alone or in conjunction with nonablative lasers in the treatment of periocular scarring and cicatricial ectropion. Additionally, they may be used to assist the transdermal delivery of antifibrotic agents. This treatment modality, although still uncommonly used to treat periocular scarring, is a promising new technique that offers many advantages. Ophthalmologists may utilize this technique to manage cicatricial ectropion.

Ko AC, Erickson BP, Ko MJ, Sayed MS, Lee WW. Ablative laser assisted topical delivery of antifibrotics in the management of cicatricial ectropion. *World J Ophthalmol* 2014; 4(2): 7-13 Available from: URL: http://www.wjgnet.com/2218-6239/full/v4/i2/7.htm DOI: http://dx.doi.org/10.5318/wjo.v4.i2.7

INTRODUCTION

Cicatricial ectropion presents a formidable clinical challenge; sequelae range from redness, tearing and foreign body sensation to potentially devastating complications, including corneal scarring, ulceration, perforation, and permanent vision loss.

Eyelid eversion is usually secondary to relative shortening of the anterior lamella. A broad range of etiologies

has been reported, but the most common include excision of cutaneous malignancy, prior lower lid blepharoplasty, thermal or chemical burns, and actinic damage in fair-skinned Caucasians[1,2]. Less commonly, cicatrizing skin diseases such as lamellar ichthyosis, scleroderma, neurodermatitis, pyoderma gangrenosum, and Grzybowski-type keratoacanthoma may be implicated[3-5]. Drug related cicatricial changes, including those caused by glaucoma drops and chemotherapeutic agents, generally resolve following discontinuation of the offending agent, but occasionally require additional interventions[6,7]. Tethering within the middle lid lamella, which includes the orbital septum, retractors and preaponeurotic fat, is also a potential cause of cicatricial ectropion, and usually occurs as the result of trauma or prior surgery.

When treating cicatricial ectropion, it is necessary to understand the fundamentals of the wound healing process. Scar formation results from mechanical, chemical or thermal insults to the deep dermis. This initiates a wound-healing cascade that progresses through inflammatory, proliferative and remodeling/maturation phases[8,9]. During the inflammatory phase, platelet activation and degranulation releases cytokines and growth factors that result in the formation of a fibrin clot, which acts as an initial scaffold for repair. This is followed by chemotaxis of macrophages, neutrophils and fibroblasts. Fibroblast growth factor 2 (FGF-2), transforming growth factor (TGF)-β and insulin like growth factor produced by macrophages then induce neocollagenesis. Fibroblasts synthesize extracellular matrix (ECM), which permits vascular ingrowth. Myofibroblasts participate in wound contracture. During the maturation phase, which can take up to two years, the ECM is degraded by matrix metalloproteinases (MMPs) and type Ⅲ collagen is replaced by a more orderly array of type I collagen[8].

There is little systematic documentation in the ophthalmic literature regarding the demographic characteristics of patients with clinically significant cicatricial ectropion. Reviewing the records of 145 patients undergoing skin grafts at the Duke Eye center, Ehrlich *et al*[10] found a male preponderance and a mean age of 75 years. Thirty five percent had undergone prior transcutaneous lower eyelid blepharoplasty, 20% had a history of Mohs reconstruction, 10% a history of facial trauma, and 5% had systemic cicatrizing diseases such as scleroderma. In 45% of patients, however, the etiology was unknown.

TRADITIONAL SURGICAL MANAGEMENT

Management typically begins with conservative measures such as massage, topical emollients or steroids, and aggressive lubrication of the ocular surface. Even if further interventions are anticipated, it can be helpful to moisten the dry and keratinized palpebral conjunctiva for a few weeks prior to restoring contact with the ocular surface.

Surgical repair is aimed at vertical lengthening of the deficient anterior lamella, but may also incorporate ancillary measures to reduce the likelihood of recurrence, such as horizontal tightening, lid retractor reinsertion, and suborbicularis oculi lift[2,11]. Depending on the etiology of ectropion, lysis of middle lamellar adhesions may also be necessary. Traditional techniques include transposition flaps from the opposing eyelid, full-thickness skin grafts (FTSGs), W- and Z-plasty with scar excision, and island flaps based on the superficial temporal artery[12].

Bipedicle myocutaneous upper to lower eyelid transposition flaps generally offer the best color and texture match. They have been subject to multiple refinements since introduced by Landolt in 1885[11,13]. A bipedicle flap has several distinct advantages over a temporally hinged unbipedicle flap including improved blood supply and improved structural support as it acts as a sling from the upper eyelid[11,13].

FTSGs are also a popular option for anterior lamellar augmentation. Matching of skin color, texture and thickness is critical to optimizing cosmetic and functional outcomes. The suitability of tissues, in descending order, includes the upper eyelid, preauricular area, postauricular area, and supraclavicular region[14]. Lack of suitable donor tissue remains the primary contraindication; burn patients and those with systemic cicatrizing conditions may be poor candidates. Given the prevalence of robust collaterals in the eyelids, necrosis and infection are rare complications. Careful hemostasis and use of postoperative bolsters, however, are necessary to reduce the risk of hematoma formation, which can rapidly devitalize a graft.

Z-plasty is useful for addressing cicatricial ectropion, but is limited to cases resulting from focal scarring. It is typically combined with scar excision or minimization. W-plasty is a related revision technique that creates a regularly irregular wound in lieu of a straight one, lengthening parallel to the original scar. Increased skin tension contributes to further hypertrophic scarring, creating a vicious cycle that can be broken by these revision techniques[9].

ALTERNATIVE TECHNIQUES

Systemic cicatrizing disease may limit the availability of viable autograft tissues. Some authors report use of groin or even penile foreskin in the setting of limited donor sites[4,15,16]. More radical departures, such as grafting mucus membranes, maternal skin, and even human skin replacements, have been described[15,17,18].

Hyaluronic acid fillers have also been used to treat select cases of cicatricial ectropion. It is thought that the filler volume physically supports the eyelid margin and acts as an injectable tissue expander, stretching the tethered anterior lamella[1]. It may be an attractive alternative in older, debilitated patients and those not desiring further surgical intervention.

APPLICATION OF LASERS FOR SCAR REVISION AND CICATRICIAL RELEASE

Laser therapy has rapidly evolved into a valuable treatment modality to improve the appearance and physical properties of cutaneous scar tissue throughout the body.

Table 1 Fitzpatrick sun reactive skin types

Skin phototypes	Sunburn	Tan
Type Ⅰ	Yes	No
Type Ⅱ	Yes	Minimal
Type Ⅲ	Yes	Yes
Type Ⅳ	No	Yes
Type Ⅴ	No	Yes
Type Ⅵ	No	Yes

The principles and treatment rationale for laser treatment of scars can also be extended to the treatment of cicatricial ectropion.

Selection of treatment candidates

Prior to proceeding with laser therapy for scar revision, several factors that are individual to each patient need to be considered. First, the patient's skin type is determined-with a classification scheme such as the Fitzpatrick scale (Table 1)-in order to stratify the patient in terms of appropriate laser settings and possible risks and side effects of laser therapy[19]. Greater skin pigmentation results in increased interference of the energy delivered by the laser, thus decreasing the amount delivered to the targeted hemoglobin and therefore the dermal scar tissue. Additionally, patients with darker skin types are at greater risk of melanin destruction which leads to postoperative skin dyspigmentation[20-22].

Caution should also be taken in patients with inflammatory, autoimmune, or infectious skin disorders. Dermal inflammation of any etiology may interfere with postoperative healing and therefore decrease the overall effectiveness of the laser treatment. Patients may experience exacerbation or dissemination of autoimmune (*e.g.*, vitiligo, lupus) or inflammatory (*e.g.*, psoriasis, eczema) conditions after laser therapy. Additionally, 0.5% to 4.5% of patients undergoing ablative laser treatment can experience exacerbation of disseminated skin infections (*e.g.*, herpes simplex virus, impetigo, mollusum, verruca)[20-22]. It has been recommended that prophylactic oral antiviral agents be administered in patients with a history of perioral herpes simplex one day before treatment and continued one week after treatment[20,22], although most physicians treat patients regardless of history if using ablative therapy.

The patient's current and previous medication usage should also be reviewed prior to initiating laser therapy. Isotretinoin and other common medications may lead to development of hypertrophic scars. Anticoagulants and antiplatelet agents should be discontinued one week prior to treatment to decrease the amount of post-treatment bruising[21].

Additional caution should be exercised in patients who have undergone previous treatments such as chemical peels, dermabrasion, or dermal filler injections[21].

Selection of laser and application

In general, lasers used for scar tissue remodeling can be divided into two major categories: ablative and nonablative (Table 2)[23,24]. Ablative lasers [*e.g.*, Erbium:yttrium-aluminum-garnet (Er:YAG) 2940 nm, CO_2 10600 nm] have a high affinity for water and causes thermal necrosis as the energy is absorbed by scar tissue. Application of this type of laser also results in an increased level of basic FGF and reduces TGF-β1, which theoretically decreases re-contraction of scars[25,26]. Treatment with this laser induces scar remodeling and improves atrophy, contracture, and texture of existing scar tissue. Commonly experienced side effects after treatment include pain, post-treatment erythema, transient and permanent hyperpigmentation, and infection[26,27]. The Er:YAG laser has a higher affinity for water than the CO_2 laser, and therefore patients typically experience less severe side effects[27].

Nonablative lasers [*e.g.*, 532-nm or 1064-nm neodymium:YAG (Nd:YAG), 585-nm pulsed-dye laser (PDL)] are chromophore-selective (*e.g.*, hemoglobin and melanin), and are thus selectively absorbed without inflicting widespread damage to surrounding tissues[27,28]. Application of the 532-nm neodymium YAG laser and 585-nm PDL results in absorption of energy by the hemoglobin, which has an absorption peak of 542-nm, that is present within the scar microvasculature. This results in ischemia, thrombosis, coagulation necrosis, and decreased collagen within the scar. At this wavelength, the laser energy is also selectively absorbed by melanin, which causes decreased scar hyperpigmentation. Additional benefits include decreased proliferation of fibroblasts[29] and deposition of collagen Ⅲ. Similar to ablative lasers, PDL also decreases TGF-β1. Nd:YAG laser treatments also causes suppression of collagen production. Treatment with nonablative lasers results in improvement of scar texture and pliability[29]. Commonly experienced side effects after treatment include post-treatment purpura and skin dyspigmentation[27].

Although there are no standard algorithms for laser treatment of cicatricial ectropion, a general approach similar to that used in treating scar tissue present in other areas of the body may be followed. In general, scar tissue is first treated with a laser that targets the microvascular component of scar tissue, which destroys the vessels and decreases the inflammation.

Next, laser energy that targets water is used to destroy and remodel the abnormal collagen fibers. Previously, ablative lasers were used to vaporize tissues at a consistent and superficial depth. However, these lasers are now typically applied in a fractional pattern, which results in the ablation of deep columns of abnormal scar tissue [microscopic thermal zones (MTZ)] that are intermixed within islands of untreated normal tissue[20]. This not only allows for a quicker recovery through rapid reepithelization and cell migration from the surrounding tissue with retained adnexal structures[30,31], it also changes collagen by modulating interleukin-1, tumor necrosis factor, TGF, heat shock proteins, and MMP. This results in the clearance of damaged collagen and the proliferation, migration, and differentiation of keratinocytes in wounds that result in the formation of new healthy collagen, resulting in more organized scar tissue with physical properties

Table 2 Common types of ablative and non-ablative lasers

	Wavelength	Manufacturer	Product name
Ablative laser			
CO_2	10600 nm	Sandstone medical technologies	Matrix LS-40
		Lumenis	UltraPulse
		Lumenis	AcuPulse
Er:YAG	2940 nm	Focus medical	NaturaLase ER
		Alma lasers gmbh/quantel derma	Burane
		Sandstone medical technologies	Whisper 3-G
		Sciton	Contour TRL
		Syneron and candela	SmoothPeel
Combined CO_2 Er:YAG laser	10600 nm/2940 nm	Sandstone medical technologies	Sandstone medical technologies cortex resurfacing work station
Nonablative laser			
Infrared range			
Pulsed energy	1319 nm	Sciton	Thermascan
Nd:YAG	1320 nm	CoolTouch	CT3Plus
		Alma lasers	Harmony XL
Diode	1450 nm	Syneron and candela	Smoothbeam
Er:Glass	1540 nm	Alma lasers	ARAMIS
Visible range			
Pulsed dye laser	585 nm/532 nm	Chromogenex	Regenlite
		Cynosure	V-Star
Long pulsed	532 nm	Laserscope aura	StarPulse
		Lumenis	VersaPulse

CO_2: Carbon dioxide; Er:YAG: Erbium:yttrium-aluminum-garnet; Nd:YAG: Neodymium:yttrium-aluminum-garnet; Er:Glass: Erbium:Glass.

and function that is more comparable to the surrounding healthy tissue[32-34].

An alternative method of treatment using the ablative CO_2 laser includes the pinhole method, where multiple small holes are made in regular intervals within the scar tissue. The delivery of focal laser energy results in a softening effect by breaking down the thick and irregular collagen bundles and may promote to more structured deposition of collagen and elastin[35]. Similar to the fractional pattern method, there is also migration of epithelial cells from surrounding viable tissue.

When using laser for the treatment of cicatricial ectropion, one should keep in mind that the eyelid skin is very thin and fragile so treatment density and power need to be greatly reduced[26] to avoid further damage of periorbital skin. In fact, cicatricial ectropion has also been reported as a complication of fractional CO_2 laser treatment and it should be used with caution in patients with a history of previous eyelid surgery or limited skin elasticity[22].

LASER ASSISTED DRUG DELIVERY

In addition to being used alone or in conjunction with nonablative lasers for treatment of cicatricial ectropion, ablative lasers may also be used in the delivery of therapeutic molecules. Although this is not a common treatment for cicatricial ectropion, the application of principles and treatment rationale for treatment of scar tissue present in other areas of the body can be used to guide treatment of periocular scar tissue.

Compared to systemic therapy, transdermal delivery of therapeutic agents has the advantages of directly targeting the affected organ, limitation of systemic toxicity, decreased drug degradation, and bypass of metabolism by the gastrointestinal and hepatic system. In order to achieve effect, the agent must penetrate the epidermis. The main barrier and rate-limiting step to drug penetration into the skin is the stratum corneum of the epidermis, which is composed of hydrophilic corneocytes arranged within lamellar sheets of hydrophobic lipid matrix. Once penetration is achieved, diffusion of the therapeutic agent encounters less resistance through the dermis (which is composed of collagen, glycosaminoglycans, and elastic fibers) and underlying subcutaneous tissue[36,37].

Principles of ablative laser use in conjunction with topical therapeutic agents

Ablative lasers applied in a fractional pattern [*i.e.*, ablative fractional resurfacing (AFR)] can be used to create vertical columns of ablated tissue at various depths. The two main lasers used for this task include the CO_2 laser and Er:YAG lasers mentioned previously in this article. The CO_2 laser creates a thicker MTZ when compared to the Er:YAG, but for both lasers the end result is the creation of regular strips of MTZs interspersed between areas of untreated skin containing appendageal units[38]. Histological studies of treated tissue have demonstrated MTZs with diameters up to 100 μm and depths up to 300 μm[39], but laser channels can be set to reach depths much greater than this. Therefore, AFR enhances transdermal delivery of therapeutic agents by disrupting the barrier function of the epidermis while allowing for rapid recovery through migration of epithelial cells from the surrounding untreated areas of skin.

The delivery of topical therapeutic agents can be augmented by adjustment of variables such as channel density and depth. Cumulative permeability of different

therapeutic agents has been studied and shows that for a fixed area of skin and fluence, an increase in the number of channels resulted in increased cumulative permeation. However, there was a nonlinear relationship between cumulative permeation and the number of MTZ channels. Within a given dosing time interval, there is a minimum number of channels required to achieve a targeted drug permeation and creating a greater number of channels will not exert a greater clinical effect[40,41].

MTZ channel depth is controlled by adjusting fluence. As expected, a greater fluence results in greater energy delivered per unit area, which results in a greater depth of penetration[40]. Thus, modulation of fluence can be used to target more superficial *vs* deeper areas of the skin. Although one would expect that cumulative permeation is directly proportional to depth of penetration due to increased exposed surface area for absorption, this has not been shown to be true in *in vivo* studies[41,42]. Oni *et al*[42] used a porcine model to demonstrate that serum levels of lidocaine and its metabolite monoethylglycinexylidide did not show a positive correlation with channel depth. At given time intervals, peak levels were significantly higher at a depth of 250 μm compared to 25, 50, and 500 μm. It has been hypothesized that the depth at which vascular plexuses are located within the tissue play a significant role in drug absorption[42]. Therefore, treatment should be tailored to the anatomical locations of vascular plexus contained within different areas of the skin.

Additional factors that may affect topical drug delivery include diffusion area of each drug from the MTZ channel in which it initially penetrated. This would require a calculation of the number and spacing of channels needed to cover any given area. For example, *in vitro* studies showed that methyl 5-aminolevulinate, a sensitizer in photodynamic therapy, diffuses 1.5 mm from each laser channel[38]. However, the distance of diffusion is likely related to physical properties (such as molecular weight, molecular size, and lipophilicity) of the drug molecule itself, and would need to be empirically determined for each therapeutic agent[37,43].

Candidate drugs for ablative laser assisted topical delivery

The use of antifibrotics in the management and treatment of cicatricial ectropion is still in its infancy and not widely practiced. Conceptually, it is a promising treatment option and warrants further investigation. Antifibrotic agents used to treat scar tissue in other areas of the body, such as interferon gamma, interferon alpha, corticosteroids, and vitamin D are theoretically good candidates for AFR assisted topical delivery[36]. Waibel *et al*[44] demonstrated that AFR assisted topical delivery of triamcinolone (TAC) greatly improved texture in hypertrophic cutaneous scars. It is likely that similar effects would be achieved with cicatricial ectropion.

The technique of AFR assisted topical delivery of therapeutic agents also opens a unique opportunity for localized delivery of unstable agents such as proteins. Local immunosuppressive effects have been shown in both *in vitro* and *in vivo* studies to deliver therapeutic antibodies that retained biological activity after delivery into the skin[45].

Additionally, antimetabolites currently used as injectable therapy for periocular scars would be good candidates for AFR assisted topical delivery. Intralesional corticosteroids such as TAC have been used to treat pathological scars since the 1960s. They are thought to disrupt inflammatory cell migration, reduce the nutrient supply to scar tissue through vasoconstriction, and interfere with the metabolic processes of fibroblasts[46]. Typical treatment regimens entail injecting a 10 to 40 mg/mL concentration at 3 to 6 wk intervals for several months or until scar improvement is noted[8,47]. Most studies report significantly improved pliability and scar volume in 50% to 100% of enrolled patients[9,48,49]. Nevertheless, recurrence rates are relatively high, ranging from 9% to 50%, and side effects include hypopigmentation, skin and subcutaneous fat atrophy, telangiectasia, necrosis, and delayed wound healing[8,46].

5-fluorouracil (5-FU) is a pyrimidine nucleotide analogue first injected off-label for scar therapy by Manuskiatti *et al*[48] in 1989[50-52]. It competitively inhibits thymidylate synthase, disrupting DNA synthesis and blocking collagen formation[8,53]. Concentrations of 40 to 50 mg/mL are typically injected at intervals similar to those for intralesional steroids, although some authors use formulations as dilute as 1.4 to 3.5 mg/mL[9,54]. Haurani *et al*[53] reported a 50% reduction in scar volume, still maintained 1 year after the termination of therapy. Fourteen percent of patients had no significant response[53]. 5-FU has a more favorable side-effect profile, with relatively low rates of local erythema, ulceration and transient hyperpigmentation[8,46]. Hematologic derangements, pregnancy, bone marrow suppression and infection are generally considered contraindications, although significant sequelae have not been reported from local injection for scar therapy[8,9,51].

Combining intralesional TAC and 5-FU was superior to either alone in a prospective, double blinded trial[47]. Wang *et al*[46] reported 62.5% efficacy for hypertrophic scar monotherapy and 92% efficacy with combination therapy. TAC is generally mixed with 5-FU in a ratio ranging from 1:3 to 1:9[9,55]. Steroids appear to reduce the inflammation caused by injection of 5-FU, minimizing pain and swelling, and the decreased concentration of TAC significantly reduces the risk of atrophy and hypopigmentation[47].

CONCLUSION

Interest in new treatment options for the functional and cosmetic sequelae of periocular scars, particularly those causing cicatricial ectropion, has been growing rapidly among ophthalmologists and oculoplastic surgeons. In addition to traditional medical management and surgical repair, ophthalmologists have drawn ideas from the dermatology literature for the treatment of scars, particularly

keloids and hypertrophic scars. This has led to the application of topical agents, injectable metabolites, and the use of ablative and nonablative lasers in the treatment of periocular scar tissue and cicatricial ectropion. Although the combination of therapeutic agents with laser treatments is in its infancy, it is a promising treatment modality for periocular scar tissue.

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MINIREVIEWS

Review of laser and light therapy in the treatment of oculofacial pathology

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Abstract

Demand for non-invasive techniques to treat oculofacial pathology has allowed for the growth and development of several new laser and light therapy modalities. These modalities include the use of intense pulsed light (IPL) and photodynamic therapy (PDT), light-emitting diode devices, as well as ablative and non-ablative lasers. Therapeutic applications in the periorbital area may involve the treatment of vascular lesions, telangiectasias, dyspigmentation, photodamage, hypertrichosis, rhytids, and scars. Laser and light-based technology offers patients treatment options that range from conservative to aggressive, allowing for choices between subtle results with little downtime or dramatic results with longer downtime. Advantages of laser treatments, as compared to traditional medical and surgical treatments, include a longer lasting effect than some of the conservative therapies and the ability to serve as a happy medium between non-invasive topical medicine and invasive surgical techniques. For patients seeking non-invasive alternatives, these modalities confer a major advantage over incisional surgery. Understanding appropriate usage, side effects, and outcomes is before treating functional and cosmetic issues. Here we present a review of current treatment modalities, their use, side effects, and outcomes.

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Key words: Intense pulsed light; Ablative lasers; Non-ablative lasers; Fractional lasers; Photodynamic therapy; Non-invasive techniques

Core tip: Laser and light treatments have become an essential addition in the oculoplastic service armamentarium for the management of different pathological oculofacial conditions as well as for aesthetic improvement. Both the unique anatomy of the periocular area, and one's individual treatment goals for the patient, must help tailor the choice of laser, the energy level used, and the depth of treatment to achieve an optimum result.

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INTRODUCTION

The demand for non-surgical treatment options for cosmetic and functional periorbital pathology has grown in recent years. Injectable soft tissue fillers[1] and neurotoxins[2] have maintained their popularity, as they are useful for addressing resting and dynamic rhytids as well as volume deficits. However, they are unable to address problems with the skin surface or quality. Chemical facial

Table 1 Light and laser applications

Type of laser/light	Specific type	Tissue target chromophore	Applications	Advantages	Disadvantages
IPL		Hemoglobin, melanin	Telangiectasias, pigmented lesions, hair removal, skin resurfacing	Not invasive/not a laser/light based	Not an option for darker skin types
PDT			Fine wrinkles, telangiectasias, hyper pigmentation	Treatment of specific areas, no damage to surrounding tissues	Pain during treatment
Ablative	CO_2	Water	Skin resurfacing, scars, lesions	Excellent results, especially in skin resurfacing	Prolonged postoperative period, increased risk for side effects (erythema, dyspigmentation)
	Er:YAG	Water	Wrinkles		
	Diode	Melanin	Hair removal, resurfacing		
Non ablative	QS Nd:YAG	Melanin	Tattoo removal, pigment lesions	Less aggressive, low risk for side effects	Less effective when compared to ablative lasers
	QS alexandrite	Melanin	Tattoo removal, pigment lesions		
	QS ruby	Melanin	Tattoo removal, pigment lesions		
	QS frequency-doubled Nd:YAG	Melanin, hemoglobin	Pigmented lesions, red tattoos		
	Pulsed dye (green)	Melanin, hemoglobin	Pigmented lesions, red tattoos, hemangiomas		
	Argon	Melanin, hemoglobin	Telangiectasias, PWS		
Fractionated	Ablative	Water	Dyspigmentation, acne, traumatic scarring, rhytides, skin resurfacing	Quick recovery	Erythema, edema, hyper-hypo-pigmentation, herpes simplex viral reactivation, bacterial infection
	Non ablative	Melanin, hemoglobin	Melasma, acne scars, hair removal, skin resurfacing		

IPL: Intense pulsed light; PDT: Photodynamic therapy; Er:YAG: Erbium-yttrium-aluminum-garnet; Nd:YAG: Neodymium-yttrium-aluminum-garnet.

peels, which vary in strength from mild alpha-hydroxy acids to intense phenol-based solutions, are an option to tighten and resurface the skin[3]. The mild peels, however, may not provide long-lasting, dramatic effects[4] and the stronger peels can not be used to treat darker skin types, can be painful, and are restricted in certain patients with cardiac conditions[5].

A multitude of laser and light-based technologies have been introduced to meet a broader range of needs. Concerns regarding excess upper or lower eyelid skin, periorbital rhytids, poor skin texture or pigmentation, presence of vascular lesions, or presence of scars may all be addressed by these modalities[6]. Current therapeutic options include light-based devices such as Intense Pulsed Light (IPL) Therapy[7], photodynamic therapy (PDT)[7], and light-emitting diode devices[7]. Laser alternatives include non-ablative[8] and ablative devices[8], both of which have the option of fractionated delivery. A newer modality that is outside the scope of this review utilizes radiofrequency energy for skin tightening and rejuvenation[6]. Each of these laser and light-based technologies are discussed below.

LIGHT AND LASER APPLICATIONS

All applications are summarized in Table 1.

IPL

IPL therapy is a non-invasive light-based technique that utilizes light in the wavelength range of 500 nm to 1200 nm to target the chromophores hemoglobin and melanin[9]. IPL has been successfully utilized to treat vascular and pigmented lesions of the oculofacial area[9], and may be used for hair removal[10] and photorejuvenation[11] as well. It is currently an FDA approved therapy for the treatment of photoaging. There is thought that IPL may be successful in reducing symptoms and improving clinical stigmata of dry eye syndrome associated with meibomian gland dysfunction in patients with facial rosacea[12]. The exact mechanism of action is unknown, but theories include obliteration of vessels leading to eyelid inflammation and/or heating of the meibomian glands, allowing for easier expression of the meibum.

IPL is administered by a flash lamp device that has the ability to emit light of multiple wavelengths. Individual filters are chosen to target preferential absorption by blood vessels or pigment, depending on the pathology requiring treatment. Unlike lasers, IPL uses a non-collimated, non-coherent light source. Moreno Arias *et al*[9] have proven that the use of different filters allows one to target red pigment for treatment of vascular lesions such as spider angiomas or telangiectasias, or melanin for

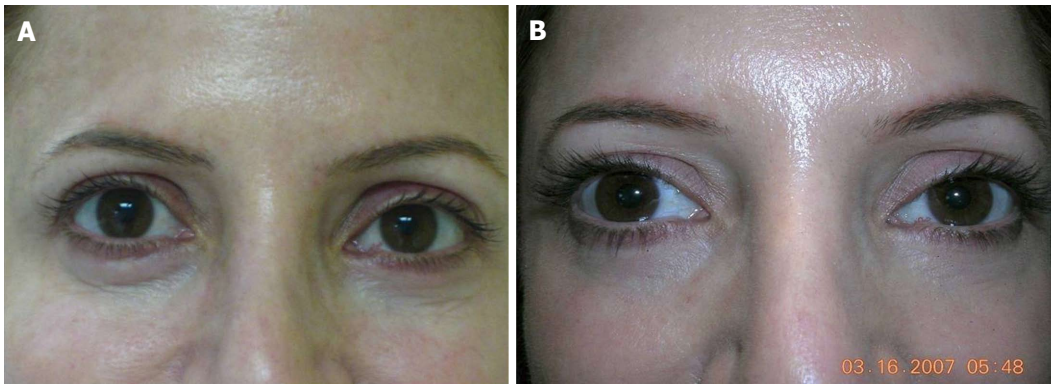

Figure 1 (A) pre and (B) post pre ablative laser treatment comparison shows improvement with reduction of the appearance of fine wrinkles, and improvement of the tone of the skin.

treatment of pigmented lesions such as actinic changes or freckles. Goldberg *et al*[11] have shown that IPL for photorejuvenation spares the epidermis and targets the dermis, generating collagen, and enabling skin tightening and contraction. Zandi *et al*[10] investigated the use of IPL for hair removal and proved that it is limited to pigmented follicles, as the target chromophore is melanin. The target chromophores for IPL also restrict its use primarily to patients of lighter skin types. Because the light is absorbed into pigment in the skin, patients with Fitzpatrick skin types V or VI are not good candidates for IPL use, and patients with skin type IV may require placement of a test spot before IPL treatment is considered[13]. Erythema of the treated areas is common for several days but is self-limited. Sun protection is required for all patients pre- and post-treatment. Uncommon side effects include pain, hypo- or hyper-pigmentation, and superficial crust or vesicle formation[14].

PDT

PDT was first used to target malignant cells by light activation of a photosensitizing agent [5-aminolevulinic acid (ALA) and ALA methyl ester (Me-ALA)] in the presence of oxygen[15]. PDT is commonly used to treat premalignant and malignant lesions such as actinic keratoses, Bowen's disease, superficial basal cell carcinoma, and other non-melanotic skin cancers. PDT has proved useful in the treatment of other inflammatory conditions, such as acne vulgaris and psoriasis, infectious lesions, such as dermatophytosis, onychomycosis, leishmaniasis, warts and molluscum contagiosum, and in benign conditions such as sebaceous hyperplasia and nevi. Recently, MacCormack[16] has proved that PDT is useful for the cosmetic treatment of fine wrinkles, telangiectasias and hyper pigmentation. One of the main advantages of PDT therapy is that it treats specific areas without damaging the surrounding tissues. Contraindications are rare, and limited to some specific photodermatoses as well as allergies to ALA and Me-ALA. Pigmented lesions are not indicated for PDT, as melanin is a fluorescence quencher and may also inhibit light penetration[16].

The most common adverse events include pain and a burning sensation limited to the term of the irradiation and several hours afterwards. Other adverse effects include photosensitivity, related to the duration of ALA or Me-ALA application and skin necrosis with consecutive scarring and hypo- and hyper-pigmentation[16].

ABLATIVE LASERS

As the desire to obtain cosmetic perfection grew, physicians began to search for other non-invasive approaches in the treatment of oculofacial pathology. In the early 1980s, ablative lasers were used more readily in the treatment of photoaging and scarring. To avoid many adverse reactions found in the first lasers, several short-pulsed, high-peak powered lasers were developed including the CW CO_2 laser and the erbium-yttrium-aluminum-garnet (Er:YAG) laser. These new lasers are better in their ability to control the depth of thermal damage at a specific pulse duration providing more accurate control and less overall damage as Alster[17] has demonstrated. The CO_2 laser, which has a higher ablation threshold and therefore targets the deeper tissues, is the most important surgical laser for cutting, vaporizing, and carbonizing. It emits a 10600-nm wavelength and is strongly absorbed by tissue water. Alexiades-Armenakas *et al*[18] in a review study have concluded that this laser is unique in that its penetration depth does not depend on melanin or hemoglobin. The CO_2 laser has proved useful in skin resurfacing and rejuvenation and even in blepharoplasty (Figure 1). This laser can also be beneficial in the improvement of fine wrinkles around the eyes. In general, this ablative laser is safer for skin types I -Ⅲ.

The Er-YAG laser, emits a wavelength of 2940 nm in the infrared range, closer to the absorption peak of water allowing for less thermal damage and quicker recovery time[19].

Ablative lasers have proved very useful in the treatment of facial rhytids, especially in the periorbital area which may not be improved with surgical face lift procedures. Scars from acne, trauma, and surgery are highly amenable to ablative laser techinques as well[18].

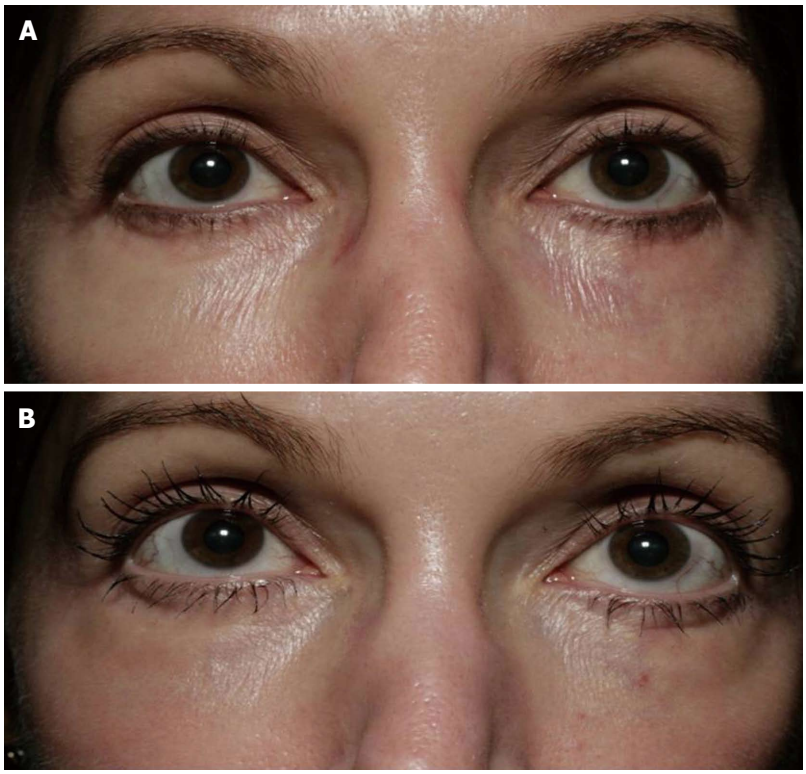

Figure 2 Visible light lasers. A: Patient demonstrating fine wrinkles prior to non ablative treatment of the upper and lower lids; B: Two weeks after a single treatment, the lids appear smoother with a subsequent reduction in wrinkles.

Absolute contraindications for laser treatment include active acne, deep acne pits or picks, and isotretinoin (Accutane) use in the past 2 years. Similarly, patients with reduced adnexal structures (*e.g.*, scleroderma, irradiation or burns) are poor candidates. History of herpetic infection is a relative contraindication only because most patients do not know their true status. Diseases with koebnerizing features, such as psoriasis or vitiligo, are also considered relative contraindications. Smokers are not excluded as treatment candidates[18].

Side effects following the ablative lasers include erythema, dyspigmentation (occurring more commonly in Fitzpatrick's skin types Ⅲ and Ⅳ), follicular, infectious, and eczematous reactions[18].

NON-ABLATIVE LASERS

Ablative lasers, although more effective, are also more aggressive and come with the potential for more side effects and longer recovery periods. This led to the development and introduction of newer, non-ablative systems. As with ablative lasers, non-ablative lasers have water as their chromophore and utilize wavelengths in the infrared range[8]. However, at these lower wavelengths water is only moderately absorbed, leading to slower heating and coagulation of the target tissue[20]. The primary goal is to stimulate collagen production and remodeling with little to no healing time. There are a number of non-ablative lasers currently available, including the neodymium-yttrium-aluminum-garnet (Nd:YAG)[21,22] and erbium glass (Er:Glass)[23] lasers in wavelengths of 1410 to 1550 nm. Visible light lasers such as the pulsed dye and pulsed 532 nm systems[24,25] (Figure 2), Q-switched Nd:YAG[26], and Q-switched alexandrite lasers also conservatively remodel with minimal downtime. They target pigment, including both endogenous melanin as well as tattoo ink, so are particularly effective at tattoo removal.

Ciocon *et al*[20] investigated non-ablative lasers, concluding that their biggest advantage is that they minimize the risks of temporary and permanent scarring by delivering dermal energy with concomitant surface cooling while leaving the epidermis intact. The wavelengths of these lasers have lower absorption coefficients than either the CO_2 or Er:YAG lasers, so a large volume of tissue can be heated without direct thermal conduction or damage. Scarring and texture change, although rare, are still risks during application[8].

Non-ablative lasers are less aggressive but adverse events such as erythema, edema, pain, burning and abnormal sensation of the eyelids may be present in the immediate postoperative period[20].

FRACTIONATED LASER DEVICES

Fractionated lasers, which are adaptations of ablative and non-ablative lasers, are designed to improve skin texture with minimal recovery time. Fractional photothermolysis was first introduced by Manstein *et al*[27] in 2004 as a modification of non-ablative laser therapy. This technology creates microscopic thermal zones of less than 400 μm diameter, extending to a depth of 1 mm or more. In between each treatment zone, the intervening tissue remains untouched. This allows for faster healing as the untreated tissue serves as a reservoir of healthy cells than migrate into the treatment zones. The treatment effect can be varied by changing the wavelength and pulse en-

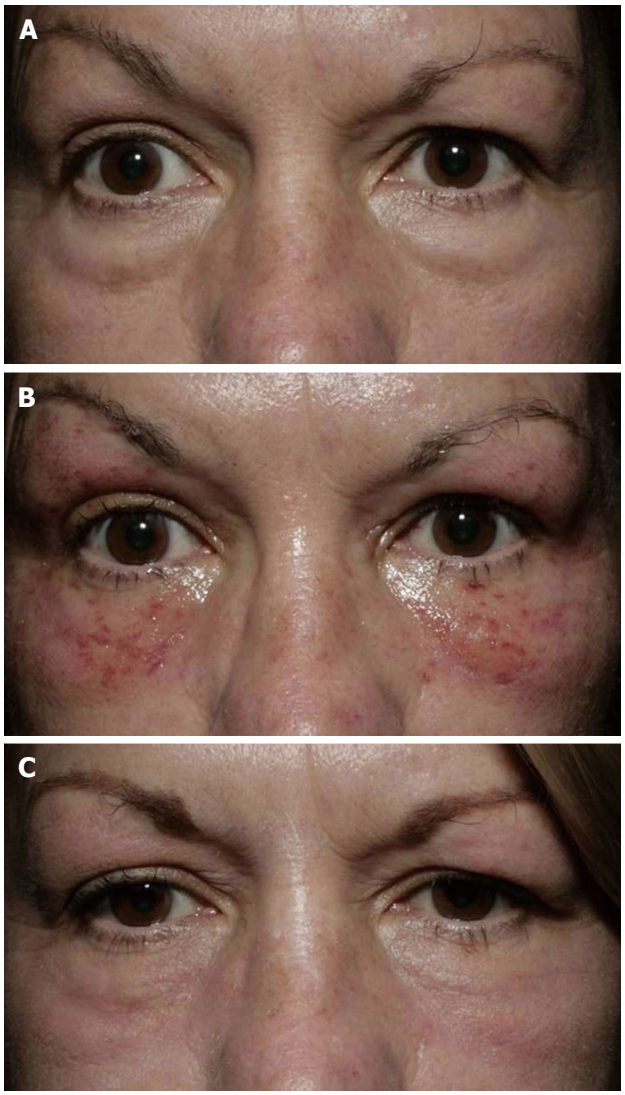

Figure 3 These lasers are useful for improvement of skin texture, dyspigmentation, acne or traumatic scarring, and rhytides around the eyes and mouth. A: Preoperative image before ablative fractional treatment of upper and lower lids; B: Three days post treatment, erythema and edema are present, skin is not completely re-epithelialized; C: One week post treatment a reddish hue to the skin is still visible.

ergy of the device[28]. In 2007, ablative fractional resurfacing devices were introduced, including fractional CO_2 and fractional 2940 nm Er:YAG lasers[29,30]. Both types of lasers induce collagenesis and epidermal turnover within several days. Since water is the target chromophore, collagen, blood vessels, and keratinocytes are all treatable. These lasers are useful for a wide array of indications including improvement of skin texture, dyspigmentation, acne or traumatic scarring, and rhytides around the eyes and mouth[27,31,32] (Figure 3). Dermal targeting allows for wrinkle effacement, scar revision and skin tightening. Targeting wider epidermal areas using ablative fractional lasers allows for treatment of photoaging changes including solar lentiges and dyspigmentation[33]. More limited data support the possible use of non-ablative fractional resurfacing for striae distensae[34-36], melasma[37-40], Nevus of Ota[33], poikiloderma of Civatte[41], and minocycline-induced hyperpigmentation[42].

In the immediate postoperative period, patients may report erythema, edema, flaking, xerosis, pruritis, bronzing, and acneiform eruptions[32]. Downtime is minimal for non-ablative devices, and may range from 1-7 d for ablative devices, during which desquamation may last for several days[32]. Rare side effects include hyper- and hypopigmentation, herpes simplex viral reactivation, and bacterial infection. Particular concern for scarring and hypopigmentation increases with higher energy fluences and more aggressive treatment, although the risks are significantly lower than those seen in fully ablative laser therapy.

LASER COMPLICATIONS AND MANAGEMENT

Although lasers target specific chromophores, the surrounding scatter and the resulting thermal effect could cause collateral damage[43]. While the main tissue chromophores are targeted, other adjacent structures that are also rich in these chromophores are susceptible to inadvertent damage.

Laser complications can range from mild eyelid swelling and erythema, skin infections, hypo and hyper pigmentation to accidental corneal injury and potentially blinding macular injury[44,45].

Laser and light injury can be prevented if certain guidelines are followed such as eye protection during treatment for the patient, the operator, the observer and the assistant. Also, laser warning signs must be placed at the entrance of the laser treatment room when lasers are operating; adequate laser safety training for personnel must be provided. Potential injury to the surrounding tissues can be minimized by adjusting the treatment parameters appropriately, using cooling devices during the procedure, applying ice packs after the procedure, and elevating the head of the bed[46].

CONCLUSION

The introduction of laser and light-based treatment has given ophthalmologists a powerful tool to manage periocular pathology and address cosmetic concerns. They offer multiple treatment options to patients seeking non-surgical oculofacial rejuvenation, and are best utilized as one component in an overall treatment strategy that may also include injectable neurotoxins, soft tissue fillers, or facial peels. Patients must be counseled regarding the limitations of these modalities, and must have realistic expectations of the outcomes. Use of this technology can provide long-lasting results, and in some cases can provide a very good alternative to surgical intervention.

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RETROSPECTIVE STUDY

Presenting clinical features of patients with vitreoretinal lymphoma

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Abstract

AIM: To assess the presenting clinical features, time from presentation to diagnosis and association with central nervous system (CNS) lymphoma in patients with vitreoretinal lymphoma.

METHODS: Retrospective case series of patients diagnosed with vitreoretinal lymphoma between 2009 and 2011 at a single center.

RESULTS: Fifteen eyes in 9 patients were included. Common presenting ocular symptoms included blurred vision (78%) and worsening floaters (44%) with an average symptom duration prior to presentation of 88.4 d (range 7-365 d). Common ophthalmic exam findings were vitreous haze (89%) and subretinal lesions (56%). The average time from presentation to diagnosis was 56.3 d (range 16-180 d). All patients were diagnosed with large B-cell lymphoma according to pathology results. Lymphoma was restricted to the eye in 33%, while 67% of patients had CNS involvement. Of the patients with secondary vitreoretinal lymphoma, 67% initially presented with CNS lymphoma while 33% initially presented with vitreoretinal lymphoma. Of the patients with CNS involvement, memory loss (67%) was the most common presenting symptom.

CONCLUSION: Vitreoretinal lymphoma most commonly presents with symptoms of blurred vision and/or worsening floaters and vitreous haze on exam. The average time from presentation to diagnosis may be decreasing with increased awareness among clinicians.

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Key words: Primary vitreoretinal lymphoma; Secondary vitreoretinal lymphoma; Primary central nervous system lymphoma; Primary intraocular lymphoma

Core tip: Vitreoretinal lymphoma is a rare, highly malignant lymphoma that can present a diagnostic challenge to clinicians. This case series was designed to identify presenting clinical features associated with vitreoretinal lymphoma.

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INTRODUCTION

Vitreoretinal lymphoma is a rare, highly malignant non-Hodgkin lymphoma, usually of B-cell origin[1]. It more commonly affects the elderly, with a reported mean age

Table 1 Demographic and clinical features of patients with vitreoretinal lymphoma

Patient No.	Age/gender	Bilateral involvement (Y/N)	Presenting ocular symptoms	Symptom onset (days prior to presentation)	Presenting visual acuity	Exam findings	Time from presentation to diagnosis (d)
1	83 yr/F	N	Cloudy vision	30	20/20	Vitreous cells	120
2	65 yr/F	Y	Worsening floaters and blurred vision	120	20/60	Vitreous cells	17
3	86 yr/F	Y	Worsening floaters and blurred vision	365	CF 1′	Vitreous haze and subretinal lesions	45
4	68 yr/M	Y	Blurred vision	Unable to determine	20/60	Vitreous cells and subretinal lesions	30
5	70 yr/F	Y	Cloudy vision	60	20/40	Vitreous cells	16
6	67 yr/M	N	Worsening floaters and blurred vision	7	20/100	Subretinal lesion	180
7	81 yr/M	Y	Blurred vision	14	20/80	Vitreous cells/ haze	30
8	58 yr/M	Y	Worsening floaters and blurred vision	21	20/150	Vitreous haze and subretinal lesions	45
9	63 yr/M	N	Blurred vision	90	20/400	Vitreous cells and subretinal lesions	24

F/M: Female/Male; Y/N: Yes/No; CF 1′: Counting fingers at 1 foot.

of 50-70[1] and is commonly considered to be a localized presentation of primary central nervous system lymphoma[2]. Delays in diagnosis are common given its morphologic similarity to vitreous inflammation. There are limited published series reporting the presenting clinical features of vitreoretinal lymphoma[3-7]. The purpose of this study is to assess the presenting clinical features including initial symptoms, symptom duration, visual acuity, exam findings, and time from presentation to diagnosis in patients diagnosed with vitreoretinal lymphoma.

MATERIALS AND METHODS

Approval for this single-center retrospective case series was obtained from the Institutional Review Board at Oregon Health and Sciences University. Patients were identified through pathology records between January 2009 and December 2011 at the Casey Eye Institute, Oregon Health and Science University. Inclusion criteria were a diagnosis of vitreoretinal lymphoma by vitreous aspirate or diagnostic vitrectomy. Nine patients met the inclusion criteria. The medical records of all 9 patients were extensively reviewed from January 2009 through May 2012.

Patient demographics including gender and age at diagnosis were assessed. Outcome measures assessed included presenting ocular symptoms, symptom duration, presenting visual acuity, ophthalmological exam findings, bilateral involvement at presentation, time from presentation to diagnosis, association with central nervous system (CNS) lymphoma and presenting CNS symptoms.

RESULTS

Fifteen eyes in 9 patients diagnosed with vitreoretinal lymphoma by vitreous aspirate or diagnostic vitrectomy were included. The median observation period was 18 mo (range 4-28 mo). Demographic and clinical features of the patients are summarized in Table 1. Of the 9 patients, 5 were male and 4 were female. The median age at diagnosis was 68 years (range 58-86 years). Presenting ocular symptoms included blurred vision in 7 patients (78%), worsening floaters in 4 patients (44%), and cloudy vision in 2 patients (22%). All 4 of the patients with worsening floaters also reported blurred vision. The median symptom duration prior to presentation was 45 d (range 7-365 d). Best corrected visual acuity at presentation ranged widely among the cohort. One patient (11%) presented with no visual impairment (visual acuity of 20/20). Three patients (33%) had mild visual impairment with a visual acuity of 20/30 to 20/60, 3 patients (33%) had moderate visual impairment with a visual acuity of 20/70 to 20/160 and 2 patients (22%) had severe visual impairment with a visual acuity of 20/200 or worse. Ophthalmic exam findings included vitreous cells/haze in 8 patients (89%) and subretinal lesions in 5 patients (56%). Four patients (44%) had vitreous haze and subretinal lesions on exam. Exam findings were bilateral at presentation in 6 patients (67%). The median time from presentation to diagnosis was 30 d (range 16-180 d).

Association with CNS lymphoma

All patients were diagnosed with large B-cell lymphoma according to pathology results. Of 9 patients, 4 patients (44%) had a history of CNS lymphoma and developed secondary vitreoretinal lymphoma. All 4 patients were treated for CNS lymphoma with one patient receiving whole brain radiation, 3 patients receiving chemotherapy, and one patient undergoing surgery. Of the 3 patients receiving chemotherapy, 2 were treated with methotrexate. At the time of vitreoretinal lymphoma diagnosis, 3 of the 4 patients were free of CNS disease. The time from CNS lymphoma remission to diagnosis of vitreoretinal lymphoma ranged from 9-36 mo. Two patients (22%) developed CNS lymphoma subsequent to the diagnosis of primary vitreoretinal lymphoma (PVRL). One patient was treated with intravitreal methotrexate and rituximab while

the other patient deferred treatment. The time from diagnosis of PVRL to diagnosis of CNS disease ranged from 3-7 mo. Three patients (33%) had PVRL without CNS involvement at the end of the study period with duration of follow-up after diagnosis of PVRL ranging from 8-29 mo. Of 6 patients with CNS lymphoma, presenting CNS symptoms included memory loss in 4 patients (67%), speech problems in 2 patients (33%), difficulty walking in 1 patient (17%), and generalized seizure in 1 patient (17%). All 6 patients were diagnosed with CNS lymphoma by magnetic resonance imaging.

DISCUSSION

Vitreoretinal lymphoma is a rare, highly malignant lymphoma that can present a diagnostic challenge to clinicians. This case series was designed to identify presenting clinical features associated with vitreoretinal lymphoma. In our cohort of 9 patients, the median age at diagnosis of vitreoretinal lymphoma was 68 years with all patients > 50 years of age at diagnosis. This is consistent with previous reports that vitreoretinal lymphoma most commonly affects the elderly[1,3-7]. 56% of patients in our cohort were male. Some previous studies have suggested a female predominance[1,3-5] while others have not[6,7]. The percentage of patients with bilateral involvement at presentation was 67%, which is within the previously reported range of 60%-90%[1,3]. The most common presenting ocular symptom was blurred vision in 7 patients (78%). Additionally, vitreous cells/haze was the most common ophthalmic finding, present in 8 patients (89%). These findings are also consistent with prior published case series[3-7]. Best corrected visual acuity at presentation was highly variable in our cohort, ranging from no visual impairment (visual acuity of 20/20) to severe visual impairment (visual acuity of 20/200 or worse). Wide variation in presenting visual acuities has been reported in a large series by Frenkel *et al*[8].

In the past, delays in the diagnosis of vitreoretinal lymphoma have been common due to its slow onset and ability to imitate other conditions. Most recently, Akpek *et al*[9] reported that the diagnosis can be achieved within 12 mo in 80% of patients. In our series, the median time from presentation to an eye care provider to diagnosis of vitreoretinal lymphoma was 30 d (range 16-180 d). This may indicate an increased awareness by clinicians of the disease. Additionally, in our cohort, 4 of the 9 patients (44%) had a history of CNS lymphoma prior to development of secondary vitreoretinal lymphoma, potentially leading clinicians to suspect the diagnosis earlier in these patients given the known association. However, among the 5 patients who presented with PVRL and no history of CNS lymphoma, the median time from presentation to diagnosis only slightly increased to 45 d (range 30-180 d). Two of the 5 patients (40%) with PVRL subsequently developed CNS involvement during our study period. According to Coupland *et al*[1], 65%-90% of patients presenting with PVRL will go on to develop CNS involvement. Our percentage may be lower given the brief duration of our study period. It is possible that our patients diagnosed with PVRL will develop CNS involvement in the future.

Our study has several limitations, including the retrospective nature of the data, the small number of patients and the brief study period. We chose to limit our study period to the prior 3.5 years (January 2009-May 2012) because we had comprehensive medical records of all patients during this time period. In the future, it will be interesting to evaluate treatment response, visual outcomes and survival rates over a longer time period in similar cohorts of patients.

In conclusion, vitreoretinal lymphoma most commonly presents with symptoms of blurred vision and/or worsening floaters and vitreous haze on exam. Visual acuity is highly variable in the presentation of PVRL. The average time from presentation to diagnosis may be decreasing with increased awareness among clinicians.

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COMMENTS

Background

Vitreoretinal lymphoma is a rare, highly malignant lymphoma. It can present a diagnostic challenge to clinicians, given its morphologic similarity to vitreous inflammation. It can develop primarily in the eye or develop in association with central nervous system (CNS) lymphoma.

Research frontiers

There are limited published series reporting the presenting clinical features of vitreoretinal lymphoma. Given the diagnostic challenges associated with vitreoretinal lymphoma, it is important to further distinguish its' presenting features to aid in timely diagnosis.

Innovations and breakthroughs

Recent reports have shown that the diagnosis can be achieved within 12 mo in 80% of patients. In this study, the average time from presentation to diagnosis was even less, suggesting increased awareness among clinicians.

Applications

By further understanding the presenting clinical features of vitreoretinal lymphoma, this study may help aid in more timely diagnosis, contributing to earlier treatment of patients with vitreoretinal lymphoma.

Terminology

Primary vitreoretinal lymphoma, formerly known as primary intraocular lymphoma, is the most common lymphoma affecting the eye, and may go on to affect the CNS. Secondary vitreoretinal lymphoma occurs when patients diagnosed with primary CNS lymphoma develop an ocular manifestation of their lymphoma.

Peer review

Paper is about primary and secondary vitreoretinal lymphoma. Generally well written and informative.

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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.

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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.

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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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MINIREVIEWS

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.

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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].

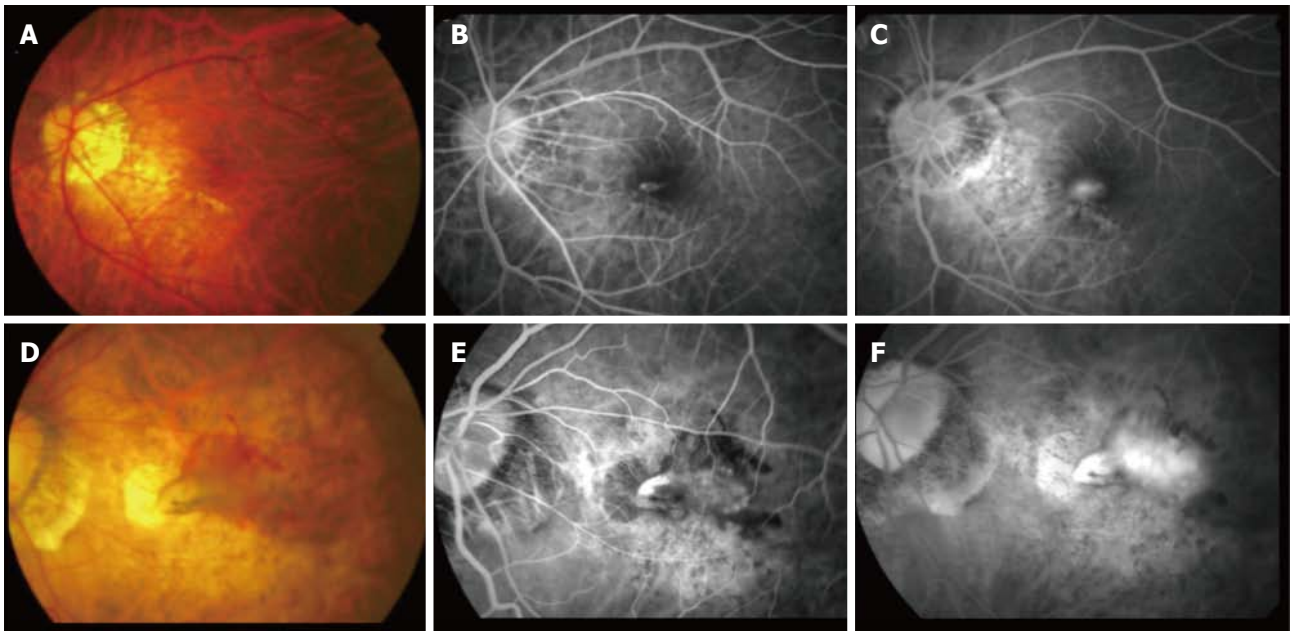

Figure 1 Clinical features of a typical choroidal neovascularization secondary to pathological myopia. (A) Color fundus photography and corresponding fluorescein angiography (FA) (B and C) showing a younger patient with a small choroidal neovascularization lesion adjacent to the lacquer crack compared 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)-

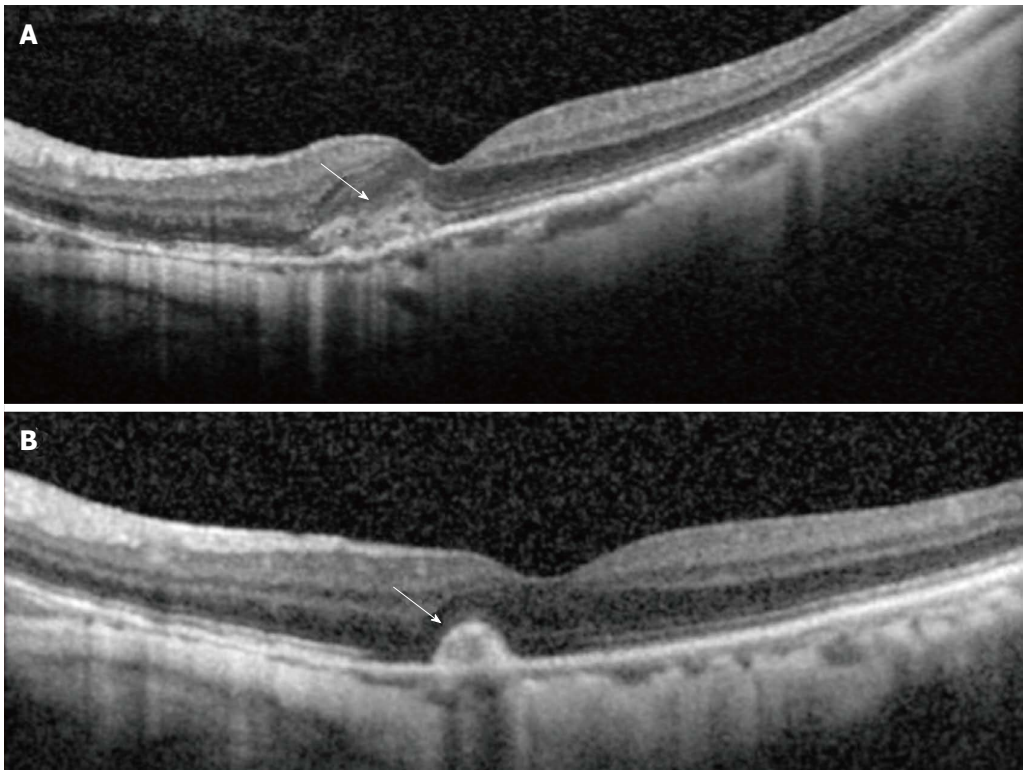

Figure 2 Optical coherence tomography showing corresponding changes in activity. (A) Shows hyperreflective lesion corresponding to a small juxtafoveal myopic choroidal neovascularization (arrow) located above the retinal pigment epithelial cell layer with minimal exudation. After 3 mo (B), the lesion 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

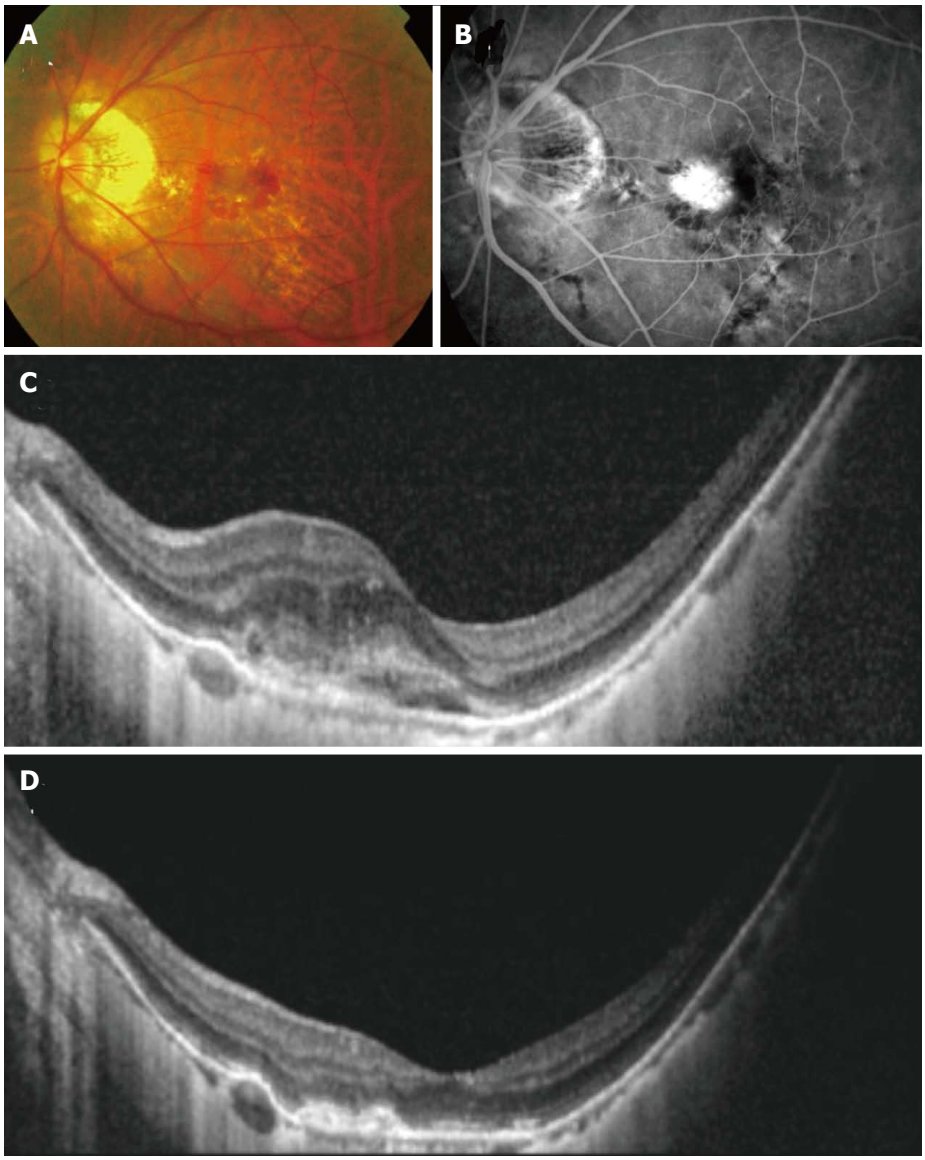

Figure 3 Resolution seen with anti-vascular endothelial growth factor treatment in myopic. Choroidal neovascularization (CNV) color fundus photograph (A), fluorescein angiography (FA) (B) and optical coherence tomography (OCT) (C) showing a larger juxtafoveal myopic CNV with significant amount of intraretinal 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-

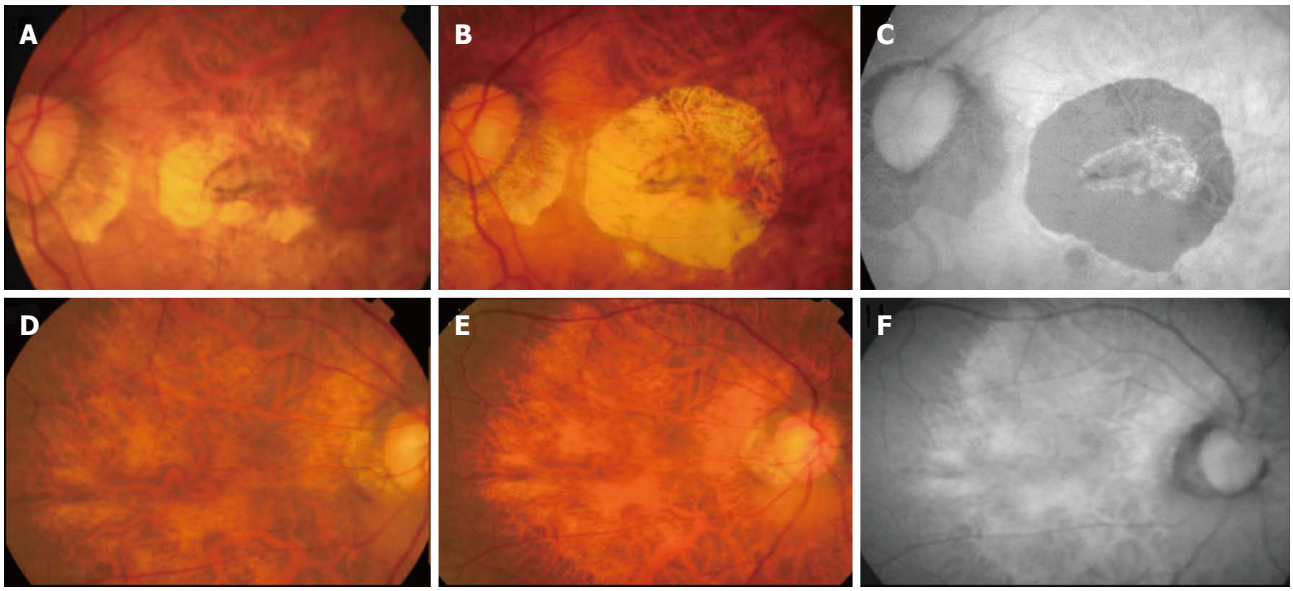

Figure 4 Progression of atrophy around treated choroidal neovascularization. Color fundus photograph (A) showing inactive choroidal neovascularization (CNV) after 1 year therapy with ranibizumab, color fundus photography (B) showing increase in CNV related chorioretinal atrophy two years later. No further 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.

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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

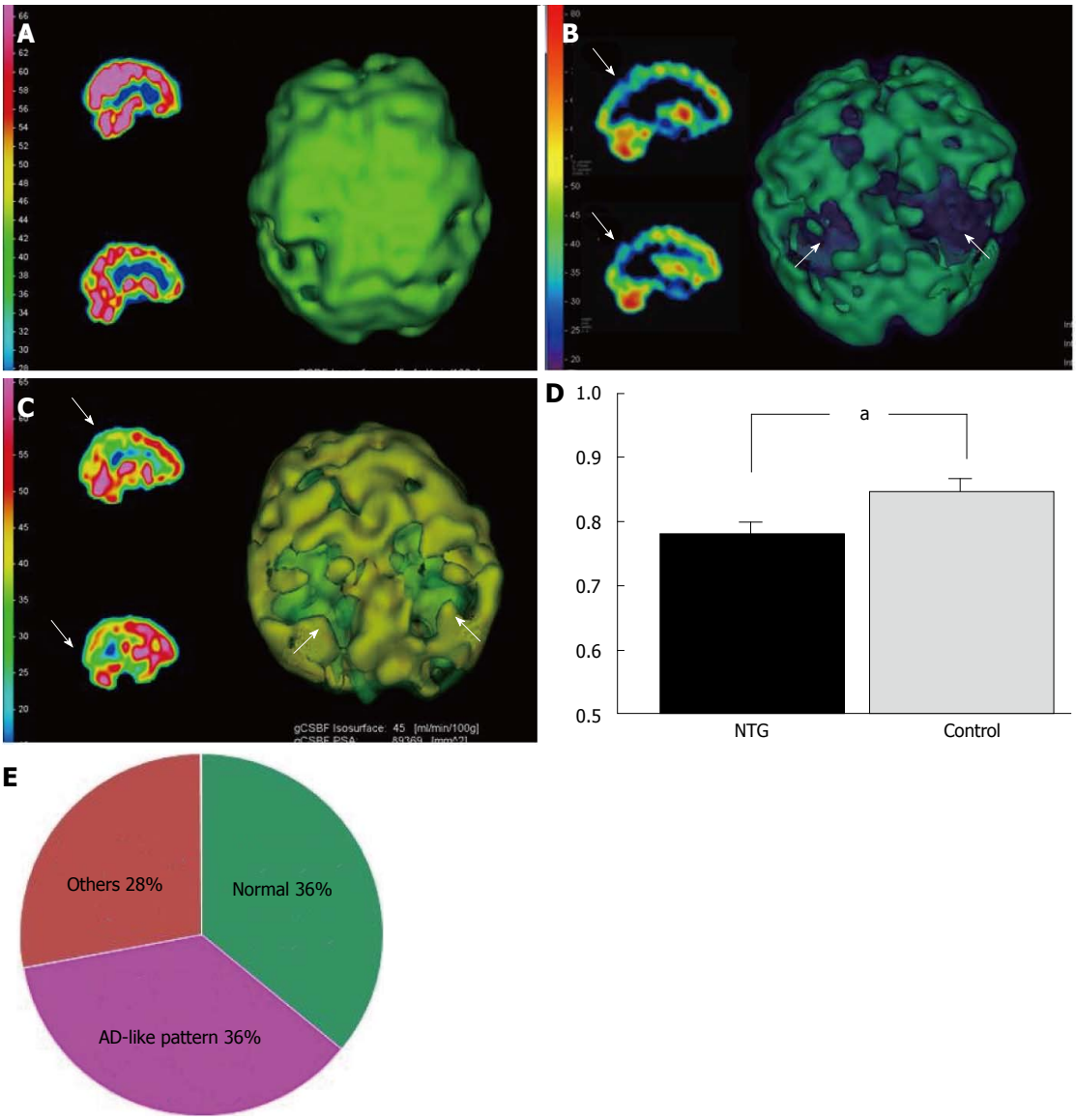

Figure 1 Representative examples of normal, Alzheimer's disease and Alzheimer's disease-like cerebral perfusion patterns by SPECT images (sagittal sections and 3D images). A: Normal pattern; B: AD pattern; C: AD-like pattern. Arrows indicate decreased CBF; D: Comparison of relative CBF in the parietal 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

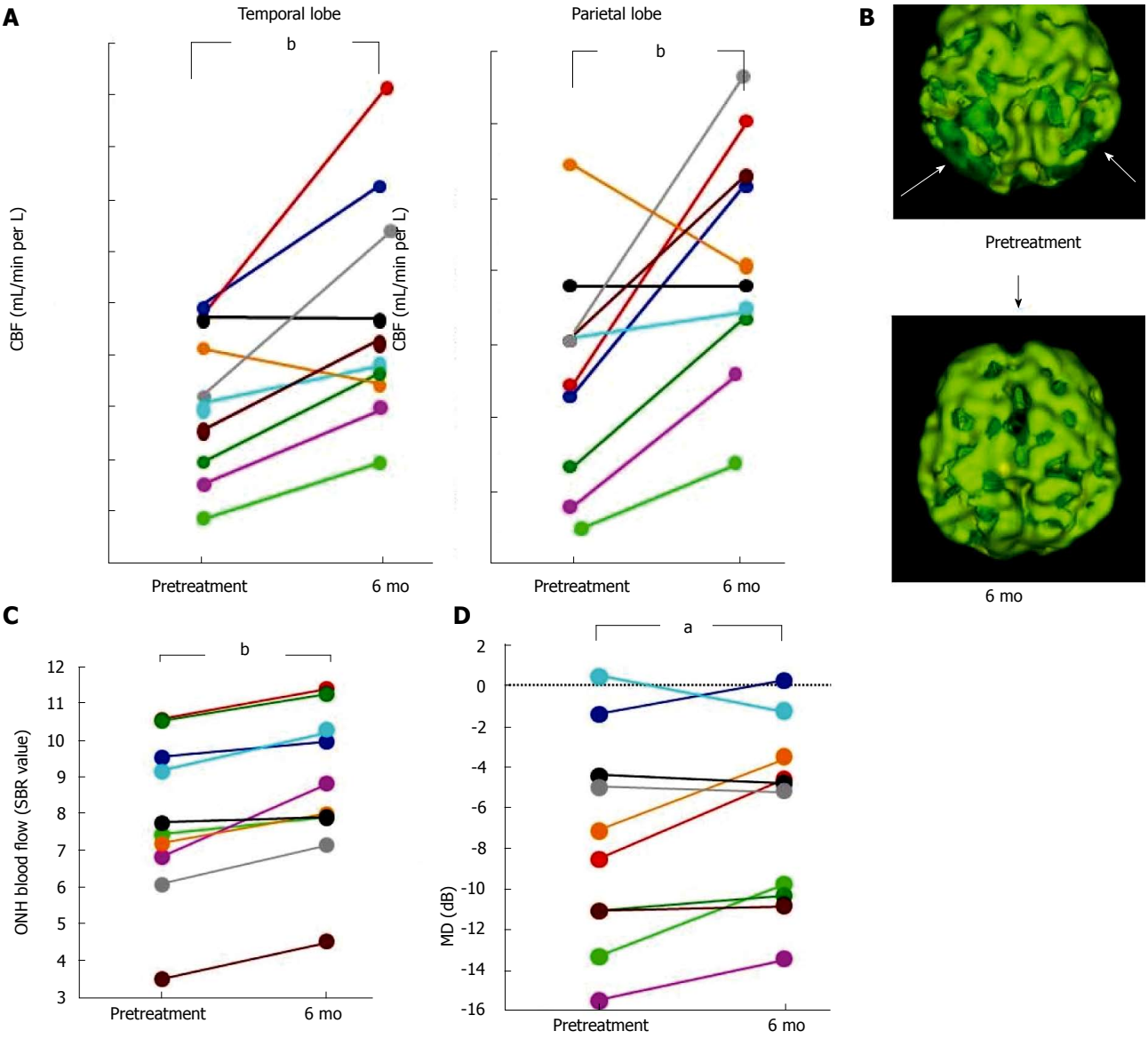

Figure 2 Changes in the cerebral blood flow of the temporal and parietal lobes (A), blood flow in the optic nerve head (C), and mean deviation (D) for each normal tension glaucoma patient after 6 mo of donepezil treatment, a representative change of SPECT images after 6 mo treatment (B). Arrows indicate 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.

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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.

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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-

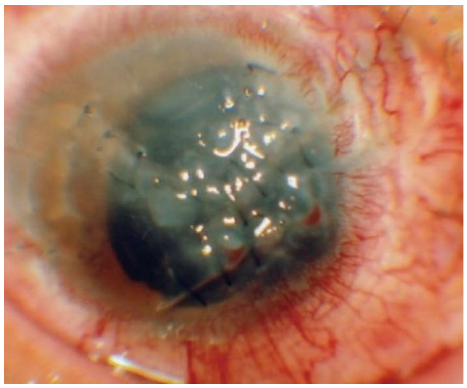

Figure 1 Anterior segment of the eye with severe penetrating corneal injury[6].

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).

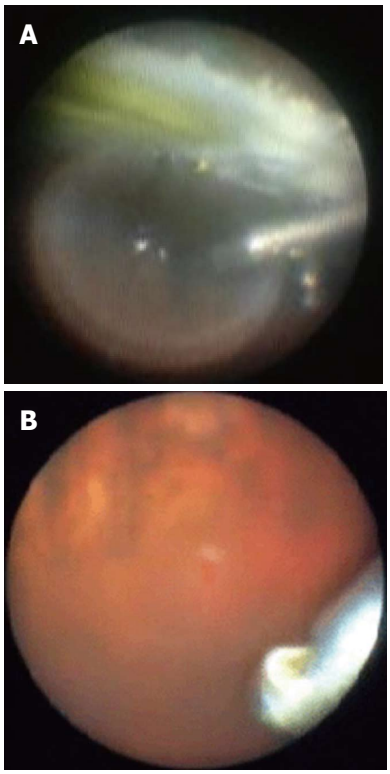

Figure 2 Intraoperative endoscopic view. A: A bubble of silicone oil and yellow IOL can be observed; B: A tiny retinal tear was identified[5].

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

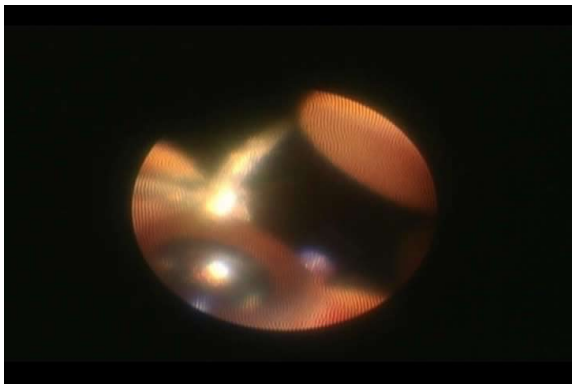

Figure 3 The direction should be arranged properly by projecting the fingers of the right hand outside of the eye.

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

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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-

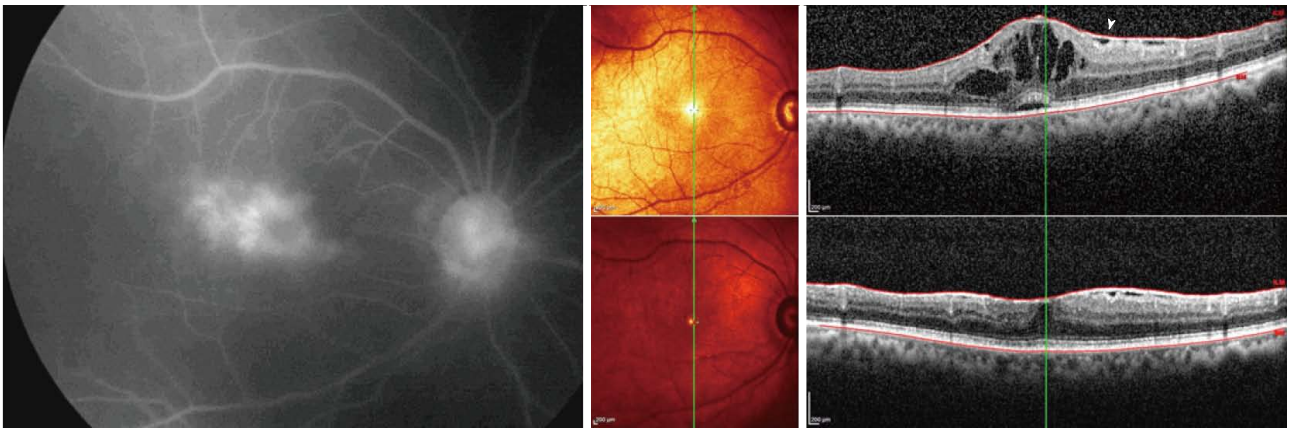

Figure 1 Uveitic macular edema. Left: Late frame of fluorescein angiogram showing dye leakage to the macular area with cystoid pattern (cystoid macular edema) due to uveitis. Upper right: Spectral-domain optical coherence tomography orientation and B-scans of the same eye showing cystoid macular edema 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.

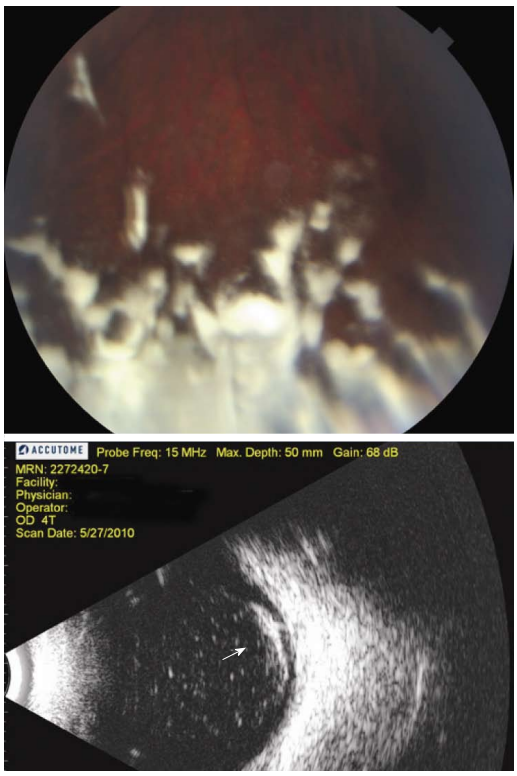

Figure 2 Intravitreal steroid treatment. Upper panel: Fundus photograph showing crystals of triamcinolone acetonide injected intravitreally; Lower panel: Ultrasound B-scan of the same eye showing crystals of triamcinolone acetonide injected intravitreally (white arrow).

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.

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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.

Wan KH, Jhanji V, Young AL. Orthokeratology lens related infections. *World J Ophthalmol* 2014; 4(3): 63-70 Available from: URL: http://www.wjgnet.com/2218-6239/full/v4/i3/63.htm DOI: http://dx.doi.org/10.5318/wjo.v4.i3.63

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

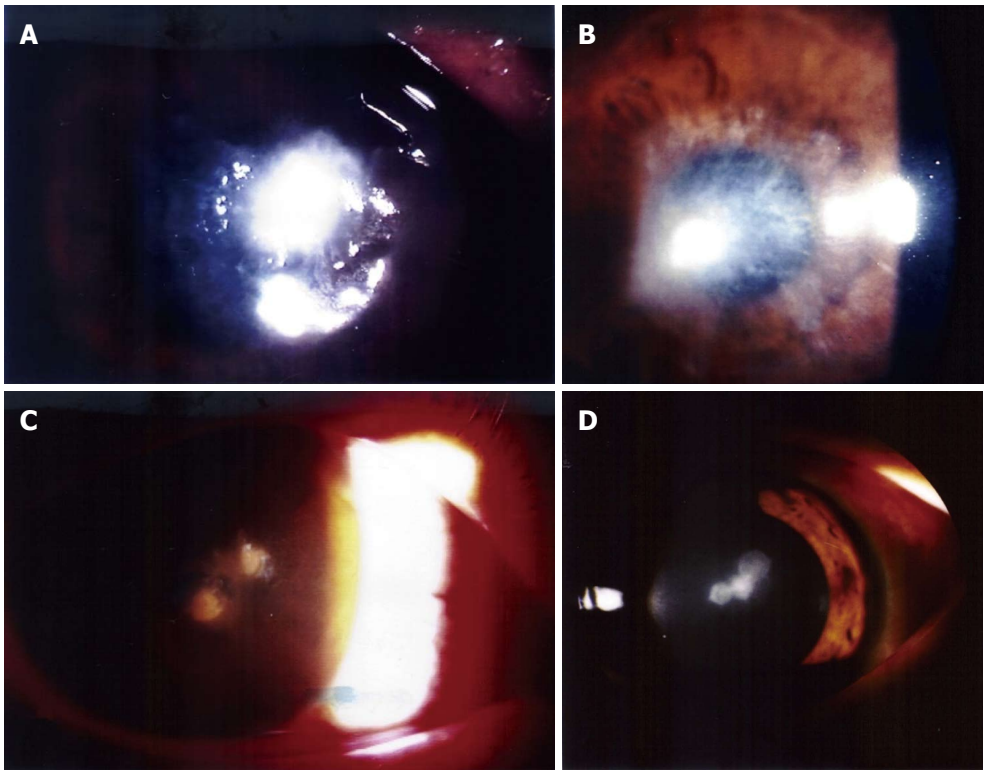

Figure 1 Microbial keratitis raises significant concerns in using overnight orthokeratology lenses. A: Presentation of a 13-year old girl who wore OKL for 36 mo with nocturnal wear at 10 h. Culture grew Pseudomonas aeruginosa; B: The 13-year-old girl with scar after treatment. Best corrected vision was 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.

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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.

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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-

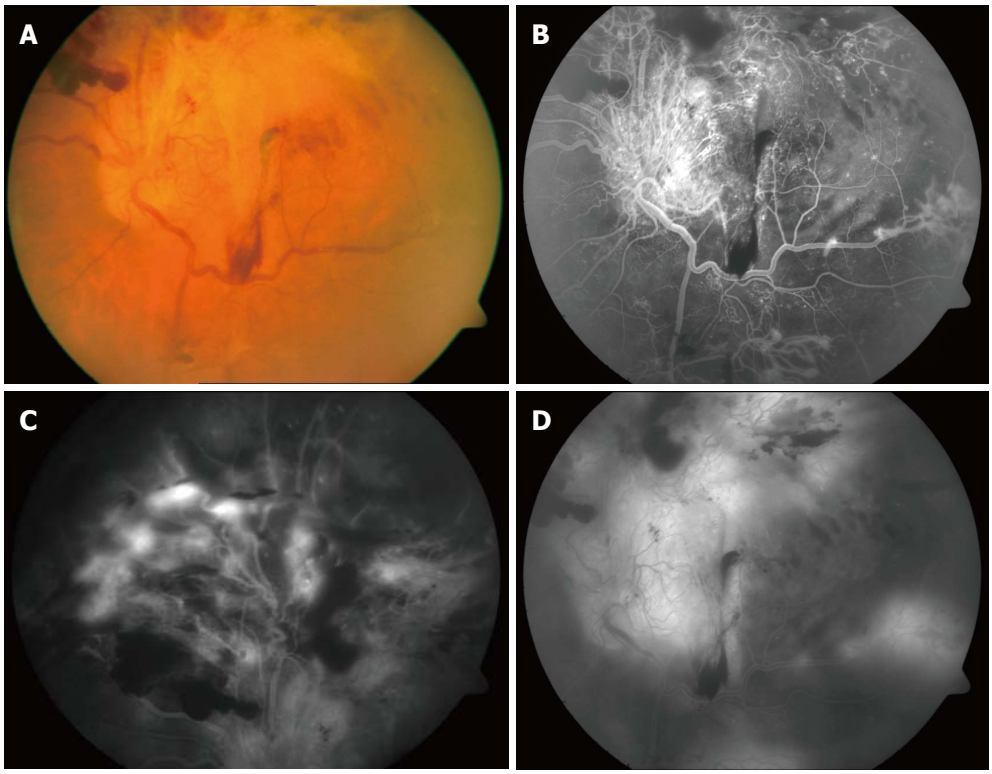

Figure 1 Preoperative images of the retina showing diabetic retinal detachment involving the posterior pole (A), the superior retina (B), and the region near the arcade (C), as well as subhyaloid and preretinal hemorrhage in the equator (D).

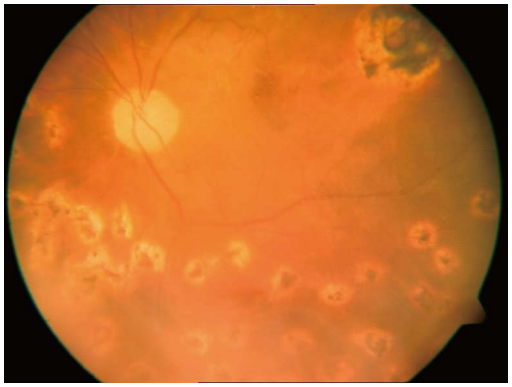

Figure 2 Postoperative image of the retina after silicone oil removal showing the retina attached and the posterior pole retinal tear treated with a laser.

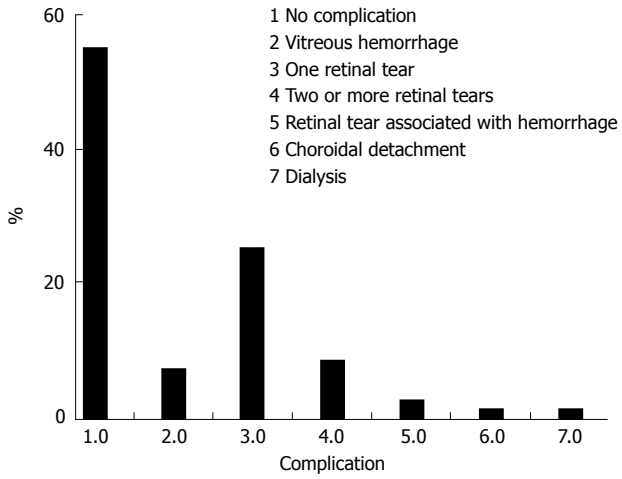

Figure 3 The percentage of intraoperative complications.

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

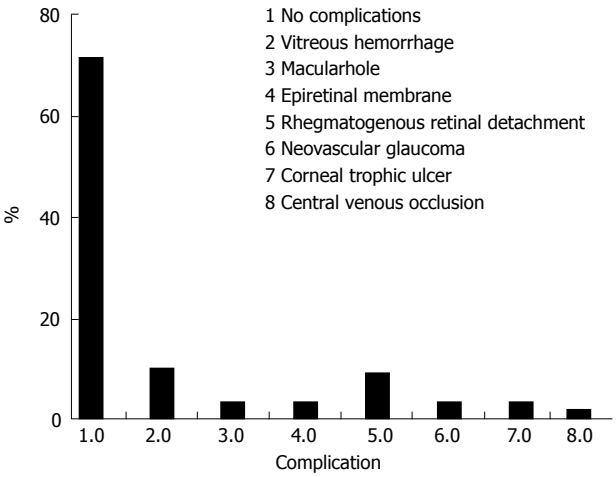

Figure 4 Histogram showing postoperative complications: Frequency distribution.

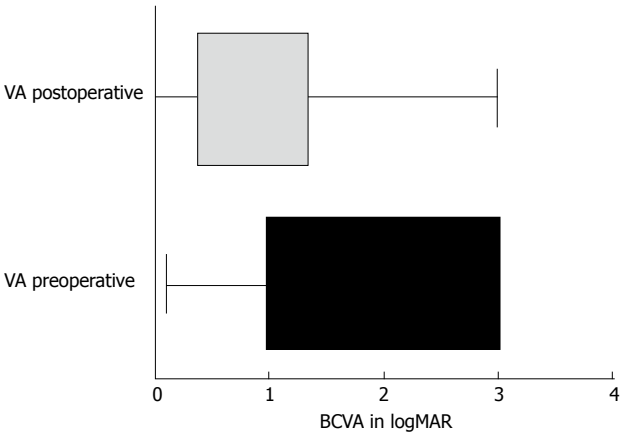

Figure 5 Comparison of pre- and postoperative visual acuity: Horizontal box-and - whiskers plot. VA: Visual acuity; BCVA: Best-corrected visual acuity.

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.

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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.

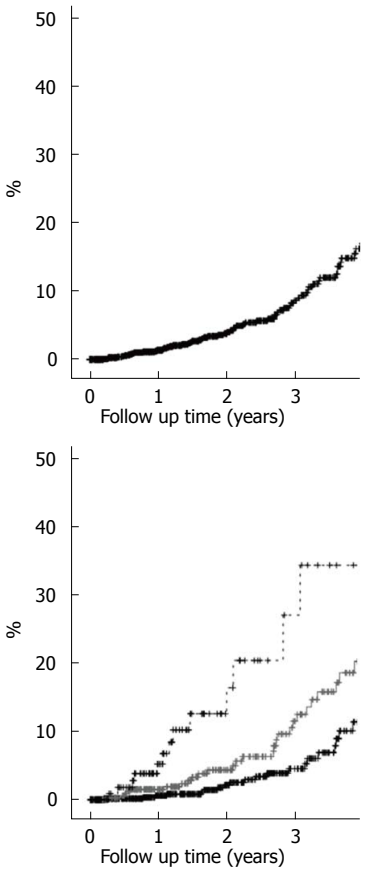

Figure 1 Kaplan-Meier analysis. A: Kaplan-Meier analysis of the cumulative probability of capsulotomy; B: Kaplan-Meier analysis of the cumulative probability of capsulotomy in eyes operated on by post-graduate year (PGY) 3 surgeons, PGY4 surgeons, and experienced surgeons (PGY5 and higher).

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.

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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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REVIEW

Pathogenesis, prevention, diagnosis and management of retinal vein occlusion

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Abstract

Retinal vein occlusion (RVO) is the second vascular retinal cause of visual loss and defined by the occlusion of a retinal vein. It is divided into branch retinal vein occlusion or central retinal vein occlusion, depending on the location of occlusion. RVO has severe medical, financial and social implications on the patients. The diagnosis of the disease is easier nowadays with the use of spectral domain optical coherence tomography and fluorescein angiography. The treatment options for RVO have changed dramatically over the past few years with the introduction of the intravitreal injections of dexamethasone (Ozurdex), bevacizumab (Avastin), ranibizumab (Lucentis) and aflibercept (EYLEA), along with the panretinal laser photocoagulation, abandoning former treatment modalities and surgical solution. This manuscript is a review of current literature about RVO with emphasize on the pathophysiology, risk factors and prevention, diagnosis and sub-group categorization and treatments including medical and surgical. Since no official guidelines are available for the treatment of RVO patients, and considering the latest developments in the treatment options, and the variety of follow-up and treatment modalities, this manuscript aims to provide tools and knowledge to guide the physician in treating RVO patients, based on the latest publications from the literature and on several of the patients characteristics.

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Key words: Retinal vein occlusion; Pathophysiology; Prevention; Diagnosis; Treatment

Core tip: Retinal vein occlusion (RVO) is the second vascular retinal cause of visual loss and is defined by the occlusion of a retinal vein. The diagnosis of the disease is easier with the common use of spectral domain optical coherence tomography and fluorescein angiography. The treatment options for RVO, has changed over the past years with the introduction of the intravitreal injections of dexamethasone (Ozurdex), bevacizumab (Avastin), ranibizumab (Lucentis) and aflibercept (EYLEA). This manuscript is a review of current literature about RVO and provides tools and knowledge to guide the physician in treating patients.

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INTRODUCTION

Retinal vein occlusion (RVO) is a retinal vascular disorder. Its main characteristic is the (partial) occlusion of the central retinal vein (CRVO) or of a branch retinal vein (BRVO) followed by the associated veins becoming engorged and dilated, intraretinal haemorrhages and edema in the retina and mainly the macula. In some cases retinal ischemia is seen which consists of areas of non-perfusion of retinal capillary bed, more or less extensive,

in the periphery or in the macular area. The ischemia is associated with deep large hemorrhages and sometimes cotton wool spots (CWS)[1-7].

RVO is considered the second vascular retinal cause of visual loss, after diabetic retinopathy, and is responsible for up to 12% of severe visual loss[8-11]. RVO occurs most commonly in middle-aged and elderly individuals of age 50 and more. The incidence of RVO is 0.7% of the population between ages of 49 and 60, and rises to 4.6% above the age of 80, with about 15%-20% of patients having CRVO and the rest BRVO[12,13]. Hemiretinal vein occlusion involves the blockage of one of the two central retinal vein trunks, an extraordinary anatomical change found in up to 20% of the population, making it a less common RVO[14].

The pathogenesis of RVO is believed to be a compression, externally, on the wall of the retinal vein in the lamina cribrosa (CRVO) or at an arterio-venous crossing (BRVO) by the adjacent artery[15]. The type of RVO and clinical picture is the result of the location of interruption. In CRVO the whole venous system, in all 4 quadrants, is involved and characterized by optic disk edema, retinal veins in all 4 quadrants become dilated and torturous, CWS, and large areas of capillary nonperfusion. Haemorrhages are a significant clinical finding in CRVO, and are found in all four quadrants. CRVO can be further divided clinically into perfused (non-ischemic) or nonperfused (ischemic). The haemorrhages in CRVO can be divided into deep retinal haemorrhages in ischemic CRVO, and superficial dot and flame-shaped haemorrhages in non-ischemic CRVO.

BRVO consists of the same clinical findings in one major retinal vein and its quadrant.

Another subtle, less frequent finding is a macular venule occlusion, which does not involve any major arcade but only a small branch draining the macula, and is frequently missed[16].

PATHOGENESIS AND RISK FACTORS

Pathogenesis

The pathogenesis of RVO is not fully understood and it appears to be multifactorial and different for BRVO and CRVO. Both types however share an arterial disease as part of the etiology as part of a systemic cardiovascular risk profile[14].

BRVO occurs at a retinal arteriovenous crossing, where both artery and vein share a common adventitia[8]. The compression of the artery on the vein results in the formation of a turbulent flow which can be demonstrated by fluorescein angiography and can lead to thrombus formation[9].

CRVO is the result of arterial compression on the vein in the lamina cribrosa where both vessels share a common fibrous sleeve. The central retinal vein usually tends to narrow in aging eyes of otherwise healthy individuals in that location, and causing a disturbance to the normal laminar flow. This disturbance increases the chance of turbulent flow and thrombus formation[17].

Several factors such as blood dyscrasia, degenerative or inflammatory disease, hypotension and obstructive sleep apnea, were suggested to take part in the pathogenesis[17-20]. In young patients under the age of 50, a complete work up is warranted to find the cause for RVO.

Macular edema (ME) is the main complication in RVO patients and is a result of an increase in retinal and macular capillary permeability and leakage leading to hypoxic environment in the retina and changes, resulting in expression of many mediators of inflammation and later to BRB break down[21,22].

Inflammation plays a major role in macular edema development with many mediators having a role including: cytokines, interleukins, chemokines, angiotensin 2, vascular endothelial growth factor (VEGF), prostaglandins, P and E-selectins, vascular cell adhesion molecule 1 (VCAM-1), ICAM-1 and particularly activation of resident cells like microglia, macrophages and neutrophils[22]. Macular edema consists of accumulation of fluid with initial swelling of the Muller cells and intra retinal fluid accumulation in the outer plexiform and inner nuclear layers.

VEGF A (VEGF-A) is a very important regulator in angiogenesis and vascular permeability and has been shown to have a key part in the pathogenesis of neovascularisation (NV) and macular edema in RVO. VEGF-A is required, along with other mediators, for blood vessel growth in pathological angiogenesis[10].

Risk factors

Several risk factors have been implicated as having a role in RVO.

Glaucoma: Open angle glaucoma is an ocular risk factor which is most commonly connected to RVO patients and plays a role in RVO pathogenesis due to compromised venous flow and stasis induction in the face of high intraocular pressures (IOP)[23-27]. This process usually occurs in the lamina cribrosa and leads to CRVO formation and increase of severity[28]. History of glaucoma may be found in up to 4.5% of CRVO patients[29]. IOP lowering medications may improve perfusion in patients with CRVO and is considered as preventive treatment in the fellow eye, which has a 10% risk of developing RVO as reported in the Branch Vein Occlusion Study (BVOS)[14,30,31].

Hypertension, diabetes mellitus and cardiovascular disease: These conditions are found in over 64% of RVO patients over 50 years old. They tend to appear more in BRVO patients than in CRVO ones[23]. Hypertension is a significant risk factor and accelerates arterial stiffness[32]. In diabetic patients, the prevalence of CRVO is equal to that of the general population, but following CRVO, diabetic patients have more disc neovascularization and are more likely to require panretinal photocoagulation (PRP) laser treatment[33].

Hyperlipidemia and hypercholesterolemia: Hyperlipidemia and hypercholesterolemia are found in over 70% of RVO patients and more prominent in RVO patients

under the age of 50[24,34,35].

Obesity and smoking: These two risk factors are associated with RVO but in a lesser degree than the prior risk factors[34,36].

Thrombophilia: The findings of high levels of homocysteine in RVO patients led to the idea that thrombophilia has a role in the pathogenesis[8,12]. This role is particularly interesting in young RVO patients, in whom the pathogenesis of the disease may differ from patients with atherosclerosis, usually older[37]. A big meta-analysis of more than 500000 patient's files indicated a RR of nearly 2.5 times for CRVO in the presence of a hypercoagulable state including homocysteinemia[32].

Two other meta-analyses showed an increased risk for RVO by 50%-60% in patients carrying the factor V Laiden mutation. Other disorders such as disturbances in antithrombin, protein C or S or the G21201a mutation were not found to be in association with RVO[15].

The relation between other conditions such as lupus anticoagulant or anticardiolipin antibodies and RVO is still not clear[8,9,38-47]. Changes in platelets reactivity may be a predisposing factor.

In a recent study on the levels of intravitreal thrombin in RVO patients compared to control eyes, a significant elevated thrombin activity and VEGF levels were found in RVO patients compared to control eyes. Higher levels were found in CRVO patients compared to BRVO ones. This led Bertelman , 2014, to the conclusion that thrombin plays a role in RVO and direct treatment should be evaluated[48].

Inflammatory disease: Inflammatory diseases can cause retinal vasculitis or inflammation and may be associated with a nearby RVO. These diseases mostly affect younger individuals, under the age of 50, and include infectious diseases such as toxoplasmosis, syphilis and tuberculosis, systemic inflammatory diseases such as sarcoidosis, Behcet's disease and systemic lupus erythematosus, and vascular diseases such as polyarteritis nodosa, Wegner's granulomatosis and Goodpasture's syndrome[49]. Therefore in patients under the age of 50, a systemic investigation is warranted for these conditions, whereas is patients over 50 years arteriosclerosis is the main cause[49].

Other risk factors: Oral contraceptives and optic disc vasculitis are a debatable risk factors and evidence is available for both sides[49-53]. The risk for RVO is reduced by 70% in women in the post-menopausal period when treated with estrogen replacing therapy, consistent with reduced cardiovascular risk profile associated with this treatment[54].

Association to obstructive sleep apnea was also reported[55] and it may double the incidence of RVO[56]. Myeloprolipherative disorders are found in 1% of RVO patients[49,57]. No relation to gender was found in RVO[14], but ethnicity plays a role with a prevalence of 3.7 per 1000 population in whites, 3.9 in blacks, 5.7 in Asians and 6.9 in Hispanics[32,58].

BRVO

Natural history

Visual acuity: In BRVO patients the initial VA is generally found to be worse than 20/40 and although it tends to improve, a final VA better than 20/40 is seldom seen[59,60]. In most patients the improvement in VA was found to be up to 28 letters[59].

In the BVOS[30,31] a significant deterioration of vision was found in 20% of untreated eyes, and in 25% of cases final VA was worse than 20/200.

NV: The incidence is believed to be relatively low but there is no meaningful data on BRVO in relation to NV and neovascular glaucoma (NVG)[59].

It is believed that with severe and extensive area of ischemia of over one-third of the retina, there is a higher incidence of NV[15].

Macular edema: Macular edema in BRVO patients develops in 5%-15% of eyes in 12 mo[59]. The GENEVA clinical trial showed an improvement in both treatment and sham groups, although the treatment group had a bigger decrease in central retinal thickness of 208 μm compared to only 85 μm in the sham group. In a subanalysis, eyes with a shorter duration of ME had a better VA outcome after treatment[61].

Fellow-eye involvement: The BVOS reported bilateral involvement in 9%[30,31]. In several other studies, bilateral involvement was reported in 4.5%-6.5% of patients at baseline[2,38,62]. Some publications indicated a similar 5%-10% bilateral involvement[15].

Management

Two objectives are to be simultaneously managed by the physician in RVO patients: (1) identification and management of the risk factors leading to RVO; and (2) the diagnosis and treatment of sight-threatening complication associated with the disease, mainly macular edema and neovascularisation.

Risk factors management: The first goal in the management of RVO is the prevention of the disease and its complications by reducing and controlling systemic risk factors. Those risk factors mentioned above are to be treated and monitored closely. Management of these factors may diminish the severity of the disease and risk of complications including fellow eye involvement. (1) systemic risk factor management: When findings of RVO are clinically present [(engorgement and dilatation of retinal veins, hemorrhages and increased retinal circulation time on fluorescein angiography (FA)] in asymptomatic patients, initiation of treatment for systemic medical risk factors, may slow or even prevent the disease progression; (2) many studies including the CVOS have shown an association between arterial hypertension or glaucoma

and RVO. The physician should exclude those conditions, or if present, treat them. All though prompt treatment is recommended in these cases, no clear evidence was found regarding the benefits of the management of glaucoma and/or reduction of arterial hypertension in regard to the visual outcome in RVO patients[14]; (3) anticoagulants, antiplatelet medications and fibrinolytic medications: Though the use of such medication can help resolve RVO or lower complication rate, several studies using those drugs (Aspirin, Heparin, Streptokinase and Warfarin) showed little to no benefit, and in patients over 55 years, a greater tendency towards vascular adverse effects[63,64]. The use of Aspirin in the management of RVO is controversial and could only be suggested, yet no proven, in the prevention of cardiovascular events[15]; and (4) hemodilution: Hemodilution was suggested by several studies as a therapy in RVO. The rationale is to lower the blood viscosity thus preventing the slowdown of blood circulation and its developing complications. The studies showing benefits of Hemodilution were monocenter studies and conducted in the 1980s and 1990s but showed significant results.

A more recent multicenter, prospective study using the recent method of hemodilution, showed some limited but positive results, and recommended the use of hemodilution in the early stage of RVO. This was shown in cases when there were no contraindications such as ischemic CRVO requiring panretinal laser photocoagulation (PRP), cardiovascular conditions such as diabetes mellitus, uncontrolled hypertension and severe cardiac or renal failure, or haematological disease such as anemia or sickle cell disease[65].

The ophthalmological RVO management: The systemic investigation and treatments as mentioned above are identical for all types of RVO. Several types of management are available today for treating patients with RVO: The dexamethasone intravitreal implant (Ozurdex) that is based on the GENEVA trial, anti-VEGF treatments as with Ranibizumab, based on the Bravo and Cruise trials.

Management of BRVO is not that different from the management of CRVO regarding the systemic cardiovascular risk factors, but the differences are that in BRVO there is a limited risk of progression, conversion to ischemic type and neovascularization.

Several targets should be held by the physician in the management of a BRVO patient: (1) systemic risk factors management; (2) localization of the area of lesion (major or minor branch); (3) assessment of the degree of nonperfusion and ischemia of the macula; and (4) treatment according to eventual complications, mainly ME and NV.

Patients with BRVO, who has a good baseline vision acuity of 20/40 or better with perfused periphery, have a favourable prognosis yet monitoring should be maintained even without intervention. The follow-up should consist of a VA examination, biomicroscopy and optical coherence tomography (OCT) in order to detect the development of ME. If necessary or when in doubt, FA should be obtained.

The follow-up should begin with monthly visits for the first 3 mo, followed by a visit every other month for a year. Patients should be instructed to seek medical assistance if they notice a VA decline which may be an early sign of ME formation.

In patients with BRVO and a deterioration of vision, physician should initiate an assessment for the presence of ME. This assessment should be done with biomicroscopy and OCT. Treatment should be initiated promptly in cases of ME.

The BVOS, a prospective, randomized, controlled clinical trial on BRVO patients, set the criteria for the use of laser photocoagulation in BRVO in order to "stabilize VA", and included patients with VA of 20/40 or less, who had ME of 4 mo or more, and absorption of macular haemorrhages[30,31].

The SCORE study, a prospective double-masked, randomized trial, concluded that grid laser photocoagulation should be used in eyes with vision deterioration due to ME secondary to BRVO[66,67]. No difference in 12 mo for VA outcome between the laser treated group and the triamcinolone treated groups (4.2 letters compared to 5.7 and 4.0 letters respectively) was seen[10]. The proportion of patients with a $\geqslant$ 15 letters VA improvement was 28.9%, 25.6% and 27.2% in the standard care group and both treatment groups with a non significant difference[10]. To add was the fact that the 4 mg triamcinolone treated group had a worse safety profile (cataract and elevated IOP).

The use of paracentral laser coagulation may lead to paracentral scotomas which can cause visual field defect which may decrease the quality of vision. The central vision field was not tested in the SCORE BRVO study, thus the conclusions are still controversial[66,67]. The new navigated pattern laser (NAVILAS) and patterned scanning laser (PASCAL) systems allow for a more accurate and effective laser treatment with less pain and treatment time[68,69].

Nowadays it is custom by practitioners to use sectorial laser photocoagulation in cases of an extensive area of nonperfusion in the peripheral retina with the development of neovascularization.

Triamcinolone Acetonide is a known treatment, from several studies on RVO, and was shown to decrease edema and angiogenesis. The visual improvement is transient because of its limited duration of intraocular availability.

The SCORE clinical trial compared the efficacy and safety of intravitreal triamcinolone in two doses, 1 mg and 4 mg, to the standard of care (grid laser photocoagulation). The drug used in the SCORE trial was Trivaris which is a sterile preservative free, intravitreal injection. In the trial no difference was seen regarding VA after 12 mo between the standard care group and the treatment groups with gaining 15 letters or more in 28.9% of the standard care group compared to 25.6% and 27.2% in the treatment groups. However, more IOP elevations and higher percentage of cataract were found in the 4 mg treatment group with 35% and 33% respectively com-

pared to 8% and 18% in the standard care group[66,67].

The SCORE study suggested that grid laser photocoagulation should still act as the standard care for BRVO patients with VA deterioration due to ME.

Since the duration of ME is of great significance, in a subgroup analysis of the SCORE BRVO trial, it was shown that patients had greater benefit with classical treatment if disease duration was < 3 mo.

Of the patients with ME over 3 mo, a third showed a 15 letter or more gain in VA in the 4 mg treatment group compared to only 15% in the laser treatment group. These findings were not found to be statistically significant but indicated the importance of duration of ME in choosing treatment.

Dexamethasone is a corticosteroid that decreases inflammatory mediators which cause ME. Dexamethasone has a short half-life and is highly soluble therefore an intravitreal implant of dexamethasone (Ozurdex) was developed so it can deliver a sustained level of the drug during up to 6 mo. This drug was studied in the Ozurdex GENEVA study, a multicenter, masked, randomized, sham-controlled, clinical trial of RVO patients with ME[61]. A prefilled single use applicator, containing 0.7 mg of dexamethasone in a sustained-release biodegradable implant (Ozurdex) was used.

Patients in this trial were treated with a first masked treatment at baseline and another treatment in as needed after 180 d. In this prospective, multicenter study, two randomized, parallel groups of the same number of patients showed a statistically significant effect on VA which persisted up to 180 d and was maximal after 60 d. The second OZURDEX injection showed a better effectiveness than the first one. Adverse effects were low rates of cataract formation and elevations in IOP. No injection related adverse effects were noted.

The primary endpoint of the GENEVA study was set to be the time to achieve an improvement in best corrected VA (BCVA) of ≥ 15 letters, and secondary endpoints were BCVA over 180 d, and central retinal thickness as measured by OCT.

Duration of ME was similar in both study groups with 16.4% of patients with ME duration of under 3 mo, 51.3% with a duration of 3-6 mo and 32.3% with a duration of over 6 mo. An important fact to notice in comparison between trials related to RVO is that the proportion of patients with ME under 3 mo duration was 16.4%, in comparison with 50%-60% in the SCORE BRVO[67], the BRAVO[70] and the CRUISE[71] trials. This fact is thought to have affected the results and made it difficult to compare trials, since resolution is thought to be higher in patients with ME of shorter duration.

A significant larger percentage of patients achieving a VA improvement of ≥ 15 letters was seen in the 0.7 mg treatment group after 30 d and throughout day 90 rather than the sham group. The best response was at day 60 with 29.6% of the 0.7 mg treatment group achieving the desired improvement and only 12.5% in the sham treatment group. In achieving at least 10 letters improvement in VA from baseline the rates were 52% for the treatment group *vs* 29.4% in the sham group. By day 180, 41% of patients in the treatment group had an improvement of at least 10 letters from baseline compared to 33% in the sham treated group[61].

The differences in BCVA between the 0.7 mg treatment group and the sham group were significant for all time points throughout the study for patients with BRVO. Mean BCVA in the treatment group improved by 10 letters at 60 d, and then declined towards 180 d with only 7 letters improvement. In the sham treatment group mean VA improved by 5 letters by 60 d and did not change up to 180 d. Patients receiving sham at baseline demonstrated a lower improvement in VA even after receiving the open-label injection of dexamethasone than patients who were treated with the drug from the beginning.

At day 60 the percentage of patients in the treatment group which had an increased IOP peaked, was 2%-3% with an IOP over 35 mmHg, 15% with over 25 mmHg, and 15% with a rise of 10 mmHg and more. Patients returned to normal by day 180. After 12 mo of study and two injections only about 1% had a pressure lowering procedure, and only 0.9% had cataract surgery. All patients with adverse effects were in the 0.7 mg/0.7 mg treatment group.

A recent post-hoc study on the GENEVA results[61] showed that treatment of ME associated with BRVO of short duration is more effective than delaying treatment. The percentage of reduced odds of gaining 15 letters with treatment at day 180 was 54% in patients with ME duration of 6 mo, 32% for ME duration was 3 mo and only 12% for the duration of 1 mo.

Retreatment with Ozurdex was studied in several studies with special emphasize on the time frame between injections. In a multi-center retrospective study[72] of 128 patients, 70 of them (54.7%) with BRVO, the mean time between dexamethasone injections was 5.9 mo after the first injection and 8.7 mo after the second injection. A ≥ 15 letter gain was seen in 28% of eyes with a central macular thickness reduction of 214 μm. Some of the patients had decreases VA before 6 mo which leads to the conclusion that patients should be monitored for the chance of deterioration before the 6-mo period.

The SHASTA study[73], a retrospective study showed similar results with a mean reinjection interval of 5.6 mo and a significant improvement both in VA and central retinal thickness (CRT). Retreatment was also studied in several other studies with a mean time between injections of 4.7-5.3 mo, all with a favourable VA outcome[74-76].

The 0.7 mg dexamethasone implant (Ozurdex) is United States food and drug administration (FDA) and European Union (EU) approved for the treatment of BRVO patients with ME.

Ranibizumab is a pan-VEGF blocker (Lucentis) which its efficacy and safety were studied in the BRAVO trial. The trial was a multicenter, randomized, double-blinded, sham controlled, phase Ⅲ study on patients with ME secondary to BRVO.

The 3 parallel groups of the trial were: standard treat-

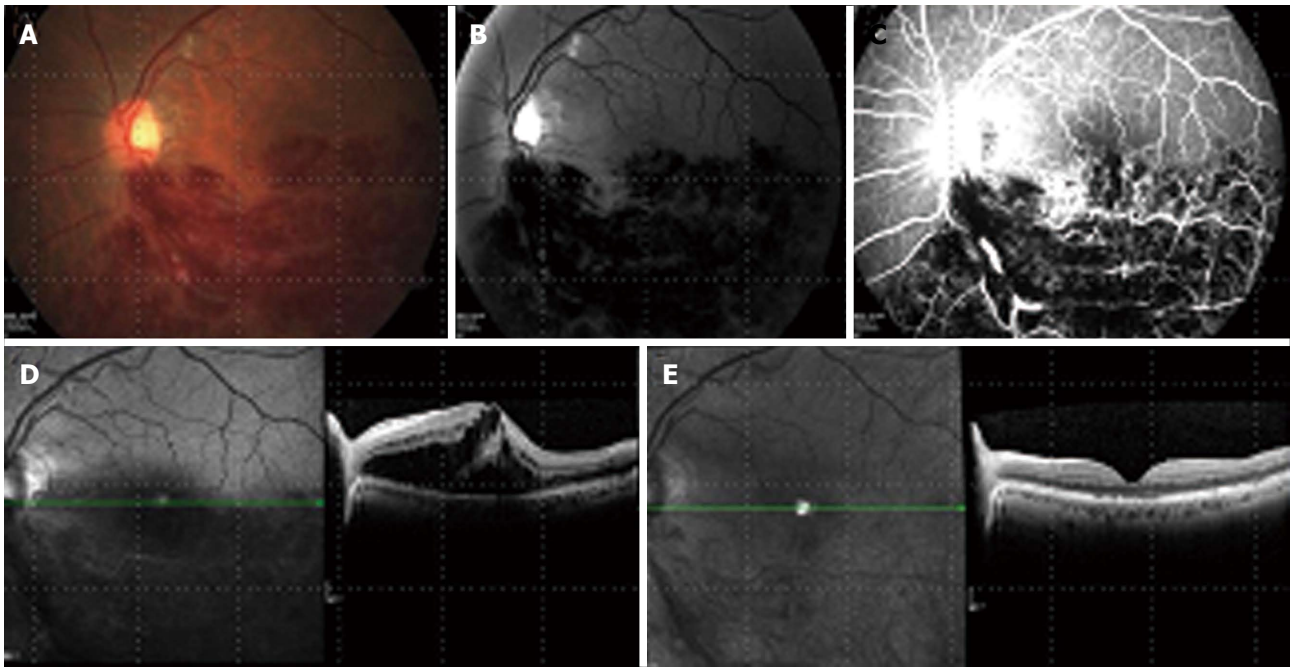

Figure 1 Left eye branch retinal vein occlusion with cystoid macular edema presented in color picture, red free and fluorescein angiography (A-C). A before treatment spectral domain optical coherence tomography (SD-OCT) of the macula (D) showing loss of foveal contour with increased central macular thickness due to many intraretinal large cystoids spaces and sub-retinal fluid accumulation. (E) SD-OCT 2 mo later, after 2 intravitreal bevacizumab injections, 1 mo apart. A normal foveal contour with some sub-foveal outer segment abnormalities. A decrease in retinal thickness back to normal and complete resolution of cystoid macular edema and sub-retinal fluid.

ment group with grid laser, 0.5 mg Ranibizumab, and a combination of grid laser and 0.3 mg or 0.5 mg Ranibizumab. According to the study's design, patients were injected on a monthly basis for the first 6 mo, followed by another 6 mo with treatment when needed. At 6 mo the treatment groups showed a better visual acuity recovery than the control group with an 18.3 letters gained in the 0.5 mg treatment group and 16.6 letters min the 0.3 mg group, compared to 7.3 letters in the sham group. This was achieved with an average of 5.7 injections. The proportion of patients achieving a ≥ 15 letters VA gain was 61.1% in the 0.5 mg group and 55% in the 0.3 mg group compared to 28.8% in the sham group[10].

In the second 6 mo period, patients were treated pro re nata (PRN), and visual improvement was maintained with an addition of only 2.7 injections. Though the change in VA was the largest in the treatment groups, the patients in the sham group also gained in VA. The BRAVO trial had ME of a short duration in about half of the patients (51.5%-53.8%)[70].

The recent RETAIN study followed the BRAVO patients in an open-label, single arm, multicenter long-term extension trial[77]. In a mean follow-up of 49.0 mo, 50% had edema resolution (no intraretinal fluid for 6 mo or more after last injection), with 76% receiving their last injection within 2 years of the first one. Final VA of 20/40 or better was seen in 80%. The mean central foveal thickness (CFT) remained under 200 μm with 88.5% with a CFT under 250 μm.

Ranibizumab 0.5 mg (Lucentis) is approved by the FDA and EU for the treatment of BRVO patients with ME.

A study conducted on Bevacizumab, in an off-label fashion off for the treatment of exudative age-related macular degeneration[78], made it commonly used medication for patients with RVO[79-85].

In a large open-label, single arm trial on the 2-year outcomes of Bevacizumab for the treatment of ME in eyes with BRVO, an improvement in VA of 0.31 logMAR was seen, with a decrease in foveal thickness of 361 μm. The response to Bevacizumab was fast and lasted throughout the year with a mean of 3.8 injections[86] (Figure 1).

No data is available on the use of pegaptanib in BRVO.

In patients with peripheral nonperfusion, assessment of the perfusion status of the macula must be done. If macula is well perfused, carrying out treatment should be as above mentioned, with grid laser photocoagulations for areas with extensive nonperfusion[60].

Even if macula is not perfused, still the treatment should be carried out in the same way, but the physician should inform the patient on the poor prognosis as related to VA.

In cases of BRVO with peripheral NV, a combined treatment of intravitreal therapy along with grid laser photocoagulation to the area of occluded vein should be promptly initiated[31].

Strategy of treatment

The randomized controlled studies on RVO have provided much information regarding treatment. An important lesson from those studies is that the duration of the disease before initiation of treatment is an important factor influencing outcome. Treatment is beneficial in any stage of the disease, including in the late stages. It has been shown that in patients with a shorter duration of

the disease, the rapid initiation of treatment may be more beneficial and the outcome is better.

Patients with BRVO should be primary screened for systemic and ocular risk factors and in case of any found, the family physician should be notified regarding the disease. The management and control of these risk factors should be fast and aggressive. Patients should be evaluated by vision assessment, biomicroscopy, measurements of IOP, and OCT. Examining the patient with FA should be done in order to find the location of the occlusive vein and to evaluate areas of nonperfusion in the periphery and the macular area. FA can also evaluate for the existence of ME or NV of the disk or retina. NV of iris or angle should be determined in a gonioscopy examination.

When periphery is perfused, and even in the face of a perfect vision, still a monthly evaluation is warranted, at least for the first 3 mo. In stable patients, the follow-up can be continued every 3 mo. All follow-up visits should include VA assessment, OCT and biomicroscopy.

In cases with decreased VA of 20/40 and under, the existence of ME should be evaluated. If ME is present, treatment should be initiated promptly. First line treatment should be with a properly approved drug, either Ozurdex with re-treatment decision according to follow-up, or with injections of an anti-VEGF drug every month for the first 3-6 mo, with additional injections depending on the progression or regression of ME.

Several characteristics of the patient may help the physician in deciding on the initial treatment. Mobility of the patient is of importance due to the necessity of a monthly visit for injections if treated with anti-VEGF. The socioeconomic status should be considered for the cost of the treatments. Pseudophakic patients can be treated with steroids with less concern. The presence of glaucoma can exclude steroids as first line treatment. Patients after vitrectomy are better treated with steroids due to their pharmacokinetics, non-compliant patients are better treated with steroids because of the need or less office visits. Younger patients should be considered for anti-VEGF because of the lens status. Patients with systemic disease such as MI or stroke are to be handled carefully with anti-VEGF. Adding to that is the physician's experience and treatment availability of the various treatments which are factors to consider.

The ongoing COMO trial is an interventional, randomized, single blind, comparison of Ozurdex *vs* ranibizumab for the treatment of BRVO. Patients with ME secondary to BRVO are randomized 1:1 to receive one of the drugs with assessments at day 7 and monthly for the first year. The hypothesis is that the effect of Ozurdex is non-inferior to that of ranibizumab in BRVO patients as assessed by change in BCVA after 1 year.

When there is non-perfusion of the periphery, and if ME is present, a rapid initiation of treatment is mandatory. First line treatment should be with an approved drug, with Ozurdex and decision about re-treatment according to follow-up, or with injections of an anti-VEGF drug every month for 3-6 mo, with additional injections based on the progression or regression of ME.

Laser treatment can still be considered for the ischemic areas in the periphery. In cases of macular ischemia the prognosis for VA improvement is generally poor even in cases of prompt treatment and ME resolution.

The development of neovascularization anywhere in the posterior or anterior chamber, no matter at what point during follow-up, should prompt the immediate treatment with sectorial laser photocoagulation to the ischemic areas. The addition of an intravitreal drug, steroids or anti-VEGF should be considered, although not proven in the trials available.

CRVO

Natural history

Visual acuity: Several studies including the Central Vein Occlusion Study (CVOS) show a poor visual outcome in patients with CRVO[7,29]. Baseline VA for CRVO is usually less than 20/40 and in most ischemic CRVO (10 disk areas or more of capillary non-perfusion), it is less than 20/200[87].

VA loss is usually more accentuated in ischemic CRVO, although VA is also poor in the non-ischemic type with more than 60% of non-ischemic CRVO patients had VA of less than 20/40 in the CVOS[6,87]. In the Ozurdex GENEVA study 92.5% of the observation group had no improvement or mild improvement (< 15 letters) after 30 d[61]. The SCORE study (Standard Care *vs* Corticosteroid for Retinal Vein Occlusion) reported 75% of CRVO eyes (both types) in the observation group with a final VA of 20/40 or worse after 12 mo[66,87].

In most studies the mean decline in VA ranged from 1 to 75 letters, although a mean improvement in VA of 1.5-12.5 letters was seen in several studies. No studies showed an improvement above 20/40[87]. In a meta-analysis of over 50 studies, the mean decrease in VA was 10 letters from baseline in 6 mo and 3 letters from baseline in 1 year for non-ischemic CRVO. In the ischemic group the decrease was of 15 letters and 35 letters accordingly[87].

In many prospective studies such as the GENEVA, CRUISE, COPERNICUS, GALILEO and others, the use of treatment for macular edema improved visual outcome largely, mainly in the non-ischemic type and changed the visual outcome of the disease in a large scale[61,71,88,89].

Alternative blood drainage formation: In BRVO, the process of venous collaterals formation is a way to facilitate the flow of blood from the vein which was obstructed to a close-by vein which is open and have normal flow. The collateral formation is the result of pressure and flow changes within the retinal veins after the obstruction[90]. Collateral formation allows reversibility of the circulation interruption and inflammation formation, and was correlated to better visual outcome. In one study VA improved from 0.22 logMAR to 0.59 in patients with collateral formation compared to an improvement from 0.24 log of the minimum angle of resolution (logMAR) to only 0.31 in eyes with no collateral formation[91].

In regards to CRVO, retino-choroidal collateral veins,

also known as optico-ciliary veins tend to develop on the optic disc. They act as an alternative drainage route for retinal blood. Some researchers believe these shunts are formatted de novo, while others hypothesise that the vessels only enlarge in the face of CRVO[92]. In a study regarding the formation of those shunts, the mean time to develop them was 6.7 mo, and most patients with those shunts did not develop anterior segment NV. The conclusion of Fuller *et al*[92] (2003), was that optico-ciliary veins are protective in CRVO patients from the development of anterior segment NV.

Conversion from well perfused to ischemic CRVO: The recognition of well perfused (non ischemic) retina and ischemic areas is best done by FA.

Conversion rates were reported in several studies to be up to 27%[87,93,94] in CRVO, after up to a 13 mo period. The ischemic conversion was described in the CVOS[6] where a total of 34% of patients converted to ischemia in the 3 year follow-up period. Of them 15% converted in the first 4 mo since disease developed[87]. Since conversion to the ischemic type can occur in up to third of CRVO patients in up to 3 years time, a long-duration, close follow-up is warranted in these cases with high clinical suspicion and performing FA and initiating treatment when conversion is suspected.

NV: NV of retina or disk secondary to an initially non-ischemic CRVO was found in up to 33% over a period of up to 15 mo[87]. As for ischemic CRVO, the incidence of NV was up to 20% over a period of 9 mo[87,95]. In some studies with no sub-division, NV was seen in up to 50% of patients after a 6 mo period[87].

The strongest predictors for NV of iris or angle were found to be visual acuity and extend of ischemic areas as seen on FA. 35% of ischemic eyes in the CVOS, developed NV of the iris or angle, compared to only 10% developing anterior chamber NV in non-ischemic eyes[29].

Ischemic CRVO is associated with neovascular glaucoma in 23%-60% of cases, and is first detected by gonioscopy. The primary finding is of a vascular network located in the trabecular meshwork and causing blockage[87]. Gonioscopy is useful and should be part of the examination regularly in all CRVO patients, but mostly in the patients with the ischemic subtype, in order to detect NV of the angle as soon as possible and allow immediate treatment with PRP for the prevention of neovascular glaucoma as proposed by the CVOS[7].

Macular edema: Most studies on CRVO enrolled patients already diagnosed with having ME at baseline. Only 2 studies reported the development of ME over time but both had only 3 eyes[87]. ME is a major complication of CRVO and associated with poor visual prognosis without treatment. Early treatment is essential since the longer the edema exists, the worse is the structural damage to the fovea[87], but even late treatment could improve VA.

In cases of ischemic CRVO resolution of ME ranged up to 73% in up to 15 mo, compared to the non-ischemic type where the corresponding proportion was about 30% by 15 mo[96,97].

Fellow-eye involvement: Systemic risk factors of CRVO patient make the fellow eye as vulnerable as the effected eye. Both eyes involvement at baseline was described in 9 studies and showed a rate of 0.4%-43% of CRVO cases[87]. 5%-10% of CRVO cases will develop RVO of any type in the fellow eye in a 3 year period[87,98-100].

Vitreous haemorrhage: The incidence of vitreous hemorrhage (VH): in CRVO patients was described in one study and was 10% in a 9 mo follow-up[87].

Management

Two objectives are to be simultaneously managed by the physician in RVO patients: (1) identification and management of the risk factors leading to RVO; and (2) the diagnosis and treatment of sight-threatening complication associated with the disease, mainly macular edema and neovascularisation.

Risk factors management: The first goal in the management of RVO is the prevention of the disease and its complications by reducing and controlling systemic risk factors. Those risk factors are to be treated and monitored closely. The management of these factors may diminish the severity of the disease and risk of complications including fellow eye involvement.

When findings of RVO are clinically present (engorgement and dilatation of retinal veins, hemorrhages, increased retinal circulation time on FA) in asymptomatic patients, initiation of treatment for systemic medical risk factors, may slow or even prevent the disease progression.

Many studies including the CVOS have shown an association between arterial hypertension or glaucoma and RVO. The physician should exclude those conditions, or if present, treat them. All though prompt treatment is recommended in these cases, no clear evidence was found regarding the benefits of the management of glaucoma and/or reduction of arterial hypertension in regard to the visual outcome in RVO patients[14].

Though the use of such medication can help resolve RVO or lower complication rate, several studies using those drugs (Aspirin, Heparin, Streptokinase and Warfarin) showed little to no benefit, and in patients over 55 years, a greater tendency towards vascular adverse effects[63,64].

The use of Aspirin in the management of RVO is controversial and could only be suggested, yet no proven, in the prevention of cardio vascular events[15].

Hemodilution was suggested by several studies as a therapy in RVO. The rationale is to lower the blood viscosity thus preventing the slowdown of blood circulation and its developing complications. The studies showing benefits of Hemodilution were mono-center studies and conducted in the 1980's and 1990's but showed significant results.

A more recent multicenter, prospective study using

the recent method of hemodilution, showed some limited but positive results, and recommended the use of hemodilution in the early stage of RVO. This was shown in cases when there were no contraindications such as ischemic CRVO requiring panretinal laser photocoagulation, cardiovascular conditions such as diabetes mellitus, uncontrolled hypertension and severe cardiac or renal failure, or haematological disease such as anemia or sickle cell disease[65].

Ophthalmological management of CRVO: The systemic investigation and treatments as mentioned above are identical for all RVO patients. The ophthalmological management differs between BRVO and CRVO. Several types of management are available today for the treatment of RVO: The dexamethasone intravitreal implant (Ozurdex) that is based on the GENEVA trial, anti-VEGF treatments as with Ranibizumab, based on the BRAVO and CRUISE trials, the recent Aflibercept, based on the COPERNICUS and GALILEO trials, and the laser treatments in specific indications.

When managing a CRVO patient it is crucial to classify it into well perfused (or non-ischemic) or non-perfused (ischemic). This classification is based upon the evaluation of capillary non-perfusion areas both at the posterior pole and at the periphery of the retina by fluorescein angiography. This classification is the basis for the treatment indications of sight-threatening complications.

In the well perfused, non-ischemic CRVO, the major sight-threatening complications are ME and the conversion into the ischemic subtype.

In the non-perfused, ischemic CRVO the major sight-threatening complications are again macular edema, usually in a more severe way, but also and mainly, neovascularization of the posterior pole [neovascularization of disc (NVD) or elsewhere (NVE)], or of the anterior segment of the eye [iris or angle neovascularization (NVI or NVA accordingly)].

The differentiation between ischemic and non ischemic CRVO subtypes can be difficult, especially at an early stage of the disease[3,5,7,29,38]. There are several clinical and functional findings that are typically found more in ischemic CRVO: acute onset of the disease, a very poor baseline VA, relative afferent papillary defect, the presence of deep and extensive intraretinal hemorrhages, the rapid formation of multiple cotton wool spots, and, as seen on FA, an extensive retinal capillary non-perfusion (more than 10 disc areas) both in the periphery and the macular region. The enlargement on FA of the foveal avascular zone is an indication of macular ischemia, and those patients usually carry a less favourable VA outcome[7].

Electroretinogram is another clinical tool to aid differentiate ischemic to non-ischemic CRVO as showed by Hayreh in 1989. In Ischemic CRVO a subnormal b-wave amplitude of < 60% of the mean value for normal individuals, or < 64%-69% of the patient's normal eye amplitude is usually found[101].

The use of spectral domain optical coherence tomography (SD-OCT) is essential in the evaluation and quantification of the amount of cystoid macular edema in RVO patients. It also provides further information regarding the location and amount of fluid in the retinal layers or in the sub-retinal space. SD-OCT showing hyper-reflective dots, especially in the outer layers of the retina, is suggestive of an inflammatory reaction and may represent disease activity[11].

Following absorption of fluid, severe ischemia is shown on SD-OCT by a decrease in retinal thickness, atrophy of the macular area and disruption of the outer retinal layers (external limiting membrane, Ellipsoid zone and photoreceptors)[11].

The integrity of several of the retinal layers, including the external limiting membrane as well as the inner segment and outer segment of the photoreceptors, is indicative of the visual prognosis. The existence of the ischemic component is shown by thinning of the retinal nerve fiber layer that can be discovered during follow up[102].

Patients with non-ischemic CRVO which have a favourable baseline VA (better than 20/40) have a good prognosis and observation only policy is acceptable. No ophthalmological treatment is compulsory, due to the lack of complications. Yet this situation does warrant a systemic investigation for hypertension, hyperlipidemia and diabetes mellitus, with risk factor management, in order to decrease the likelihood for complications such as ischemic conversion, or fellow eye involvement. Ophthalmological risk factors such as glaucoma should be ruled out or treated. Close and prolonged follow up must be suggested in order to detect progression to the ischemic subtype as early as possible[25,27].

Monitoring these patients closely with OCT, VA assessments and biomicroscopy is essential for early identification of ME and/or conversion to ischemic CRVO. An addition of FA is warranted when progression cannot be assessed properly, or it is doubtful, and when the physician needs to assess the amount of retinal ischemia.

Monitoring these patients is suggested be done every month for the first 3 mo, followed by every other month for the first year. Gonioscopy has been suggested during this follow-up. Patients should be informed to be aware of their vision, and return promptly for an examination with every deterioration of visual acuity, which may be a sign of macular edema.

In patients with non-ischemic CRVO and poor VA, physician should assess the macula for the presence of ME, and in case of its presence, an immediate treatment should be initiated.

Treatment nowadays is indicated in eyes with non-ischemic CRVO with macular edema and a VA of 20/40 or worse[38].

The CVOS showed that no statistically significant VA benefit was seen with laser photocoagulation treatment, though improvement of the macular edema was seen. This finding was with the exception of the younger patient population[103]. Because of these findings, grid laser photocoagulation is no longer indicated for that purpose.

Corticosteroids are used in CRVO with ME due to

their ability to decrease capillary permeability and inhibit inflammatory reaction and expression of inflammatory mediators, and affect the metabolism of most of inflammatory mediators including VEGF.

Triamcinolone Acetonide in a corticosteroid preparation containing benzyl alcohol and was used to treat CRVO patients in an off label fashion (Kenalog*; Squibb). Several studies have showed the benefits of Kenalog for the treatment of patients with ME secondary to non-ischemic CRVO[104]. Kenalog* is known to have some side effects including cataract development and progression and raised IOP. The benzyl alcohol component in the preparation was also associated with sterile endophthalmitis.

The multicenter SCORE CRVO study[67] showed the beneficial effects of a preparation of preservative free intravitreal triamcinolone acetonide, (Trivaris; Allergan), for the treatment of patients with ME secondary to non-ischemic CRVO[105]. This study showed that the odds of reaching a ⩾ 15 letters gain in VA, were 5 times better in both the 1 mg dosage group and the 4 mg dosage group than the observational arm (26.5%, 25.6% and 6.8% respectively)[10]. No difference was seen between both treatment groups. The 1 mg regiment had a better safety profile rather than the 4 mg group in regards to cataract formation, IOP elevation, disease progression and the necessity for surgery. Trivaris is nowadays FDA approved.

The use of Triamcinolone acetonide is rare nowadays as newer better treatments are available.

Dexamethasone is a potent corticosteroid that is known to decrease the expression of inflammatory mediators exhibited in ME including VEGF. Dexamethasone is intravitrealy injected as a slow release, biodegradable implant (Ozurdex; Allergan), allowing up to 6 mo of medication in the vitreous. The use of an implant is mainly due to dexamethasone being highly soluble and with a short half-life when in the vitreous. The effect of Ozurdex on RVO with ME was studied in a multicenter, randomized, sham-controlled clinical trial (the GENEVA study)[61]. A disposable applicator prefilled with 0.7 mg of dexamethasone in a polyglycolate-acetate implant to induce slow release of the drug, is used for the insertion of the drug into the vitreous cavity.

The GENEVA study was a prospective, multicenter, sham-controlled study which included 3 identical, randomized, parallel groups treated with either 0.35 mg or 0.7 mg dexamethasone or sham treatment (needless applicator). In the second 6 mo of the study, the open-label treatment (second injection), all patients eligible for treatment received the 0.7 mg implant. The primary endpoint of the study was the time to achieve a ⩾ 15 letter improvement on BCVA. The secondary endpoints of the study included the BCVA over the whole 6-mo period, the central retinal thickness and the safety profile of both dosages.

The study resulted in that the 0.7 mg dexamethasone implant (Ozurdex) showed an improvement in VA with a peak effect after 60 d, followed by a decline towards the baseline VA after 180 d. After 60 d the proportion of patients achieving the primary endpoint was 29.3% and 28.5% in the 0.7 mg and 0.35 mg treatment groups, compared to only 11.3% in the sham treatment group. At 180 d the proportions were 26.4%, 19.4% and 17.0% respectively. Over a 1 year follow-up, VA improvement was achieved with a second injection after 180 d. OCT demonstrated an anatomical improvement in macular edema[61].

In regards to safety issues cataract rate was low with 7.3% in the treatment group, and so was the rate of IOP increases, 4% with a peak over 2 mo. In all cases pressure declined throughout the follow-up period, especially if treated with anti-glaucomatous topical treatment. Treatment, if given, was ceased by 180 d after implant injection. No adverse effects, regarding the injection, were noted[61].

A major conclusion from the GENEVA study was that early treatment of ME is much better than delayed treatment in regards to vision improvement. A retrospective review of the study groups has shown that eyes treated within 3 mo from onset of ME showed a better improvement of VA than eyes treated after more than 90 d[15].

A more recent post-hoc analysis of the GENEVA study, regarding the onset and duration of BCVA improvement in eyes treated with Ozurdex, showed an improvement of ⩾ 15 letters in 10% of the treatment group as soon as 7 d post treatment. The duration of a ⩾ 3 lines improvement was 60-90 d[106].

Retreatment with Ozurdex was studied in several studies with special emphasize on the time frame between injections. In a multi-center retrospective study[72] of 128 patients, 58 of them (45.2%) with CRVO, mean interval between Ozurdex injections was 5.9 mo following the first injection and 8.7 mo following the second injection. A ⩾ 15 letter gain was seen in 48.8% of eyes with a central macular thickness reduction of 355 μm. Some of the patients had decreases VA before 6 mo which leads to the conclusion that patients should be monitored closely for the chance of deterioration before the 6-mo period.

The SHASTA study[73], a retrospective study showed similar results with a mean reinjection interval of 5.6 mo and a significant improvement both in VA and CRT. Retreatment was also investigated in several other small studies with a mean time between injections of 4.7-5.3 mo, all with a favourable VA outcome[74,75].

A retrospective study on 15 eyes with ME secondary to CRVO compared the efficacy of Ozurdex treatment in vitrectomized *vs* non-vitrectomized eyes[107]. The study demonstrated both groups had a significant improvement with no significant difference between groups in regards to VA improvement and CMT reduction. Conclusion is to be made that Ozurdex is effective in both vitrectomized and non-vitrectomized eyes, and the absence of vitreous does not alter the pharmacodynamics of the drug, therefore making it suitable even in eyes after pars plana vitrectomy.

Ozurdex has the FDA and EU approval and is licensed for the treatment of patients with ME secondary to non-ischemic CRVO. The GENEVA study suggests

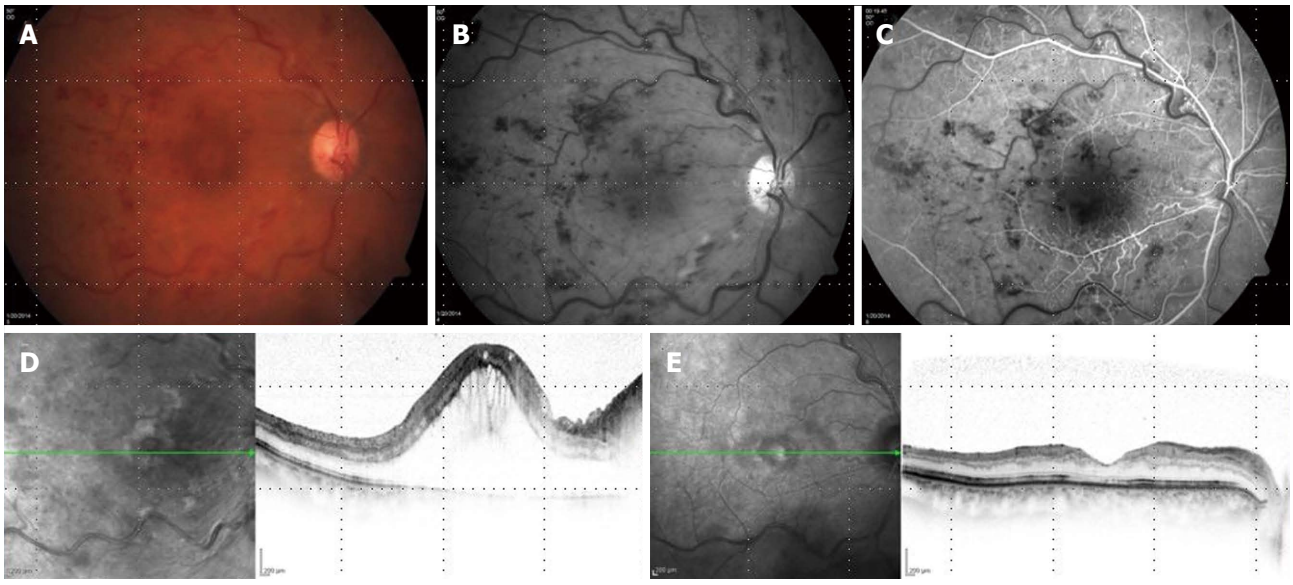

Figure 2 A non-ischemic right eye central retinal vein occlusion with cystoid macular edema in color picture, red free and fluorescein angiography (A-C). A before treatment spectral domain optical coherence tomography (SD-OCT) of the macula (D) showing loss of foveal contour with increased central macular thickness due to many intra-retinal large cystoids spaces and sub-retinal fluid accumulation. (E) SD-OCT 3 mo later, after 3 intravitreal bevacizumab injections, 1 mo apart, showing normal foveal contour with a decrease in retinal thickness to normal and complete resolution of cystoid macular edema and sub-retinal fluid.

that the implant may be considered a first-line choice in the treatment of ME secondary to CRVO.

Ranibizumab is a pan-VEGF blocker (Lucentis; Novartis) which showed effectiveness in patients with ME secondary to CRVO in the CRUISE trial[71]. In the first 6 mo of the study, ranibizumab was injected every month in two doses (0.3 and 0.5 mg) and yielded a VA gain of 12.7 and 14.9 letters, respectively, compared to 0.8 letters gained in the sham injections group. The proportion of patients achieving a ≥ 15 letters VA gain was 47.7% in the 0.5 mg group compared to 16.9% in the sham group. The effect of ranibizumab was noticed as soon as 7 d post first injection with a 9 letter improvement in the treatment group which was significantly better than the sham group[65]. In relation to the anatomical change mean CFT was significantly reduced at 6 mo in 433-452 μm in the treatment groups compared to only 162 μm in the sham group[71].

Following treatment in the first 6 mo, all patients continued in an extension for another 6 mo of monitoring and therapy PRN. The 12 mo results of the study concluded that the VA improvement showed in the first 6 mo could be maintained. Earlier treatment after ME diagnosis may bring a better functional improvement in retinal thickness than delayed therapy.

The recent RETAIN study followed the CRUISE patients in an open-label, single arm, multicenter long-term extension trial[77]. In a mean follow-up of 49.7 mo, 44% had edema resolution (no intraretinal fluid for 6 mo or more after last injection), with 71% receiving their last injection within 2 years of the first one. VA improved in 15 letters or more in 53.1%, with 43.8% having a final VA of 20/40 or better. The CMT remained as it was in the end of the CRUISE trial with a mean of 420 μm reduction.

Ranibizumab is FDA and EU approved for the treatment of ME in patients with CRVO.

Bevacizumab is a pan-VEGF blocker (Avastin; Roche) which is not licensed for intraocular use. A prospective, randomized, double-masked clinical study on Bevacizumab compared to sham in patients with ME secondary to CRVO was conducted on 60 eyes with a 1:1 randomization[108]. At the 6-mo follow-up time 60% of the study group gained ≥ 15 letters compared to only 20% in the sham group. The BCVA improved by 14.1 letters compared to a decrease in 2 letters in the sham group and the decrease in CRT was 426 μm compared to 102 μm. No residual edema was found in 86.7% of the treatment group compared to 20% in the sham group. No rubeosis was developed in the treatment group and no safety concerns were detected.

In a 6 mo extension of the study all patients received Bevacizumab every 6 wk. The percentage of patients with a ≥ 15 letters gain did not change in the primary treatment group, but in the sham group it rose to 33%. The mean VA improved in both groups to 16 letters in the treatment group compared to 4.6 letters in the sham group. In the latter, a further decrease in CRT was noticed to a total reduction of 404 μm. No rubeosis or safety issues were found in both groups in the extension trial[109].

Many other uncontrolled studies have reported that the intravitreal injection of bevacizumab may lead to VA improvement and regression of ME[110,111]. Long term outcomes and safety data is non-conclusive because of the variations in treatment regiments between those studies. Bevacizumab is less expensive than other anti-VEGF treatments making is widely used (Figure 2).

Pegaptanib is a selective anti-VEGF blocker (MACUGEN; Pfizer) which was investigated in a multicenter randomized study as treatment in RVO. Patients with ME

associated with CRVO were randomized to receive either a sham injection or 0.3 mg or 1 mg of pegaptanib sodium. The phase Ⅱ trial showed that 0.3 mg pegaptanib administered every 6 wk caused an improvement in VA of 7 letters, over a 6 mo follow-up[112]. Due to the vast use of bevacizumab and ranibizumab, pegaptanib is not frequently used.

Aflibercept is a VEGF Trap-Eye (Eylea; Regeneron) protein comprising of the second domain of VEGF receptor 1 and the third domain of the VEGF receptor 2 fused to the Fc domain of immunoglobulin G1. Its binding affinity for VEGF is greater than that of either Ranibizumab or Bevacizumab.

Aflibercept was studied in the COPERNICUS which is a 2-year, phase 3, prospective, randomized, double-masked, multi-center study of aflibercept compared to sham injection[88]. Patients were assigned randomly in a 3:2 ratio to receive aflibercept 2 mg or sham injection every 4 wk for a 24 wk period. Between weeks 24 and 52 patients were treated according to specific retreatment criteria based on VA and CRT on OCT. The second year treatment was PRN based.

VA outcome was significantly better in the treatment group with 56.1% of eyes treated achieving a ≥ 15 letter VA improvement compared to 12.3% in the sham group. 93.9% of treated eyes gained 10 letters or more compared to 52.1% in the sham group.

The improvement in VA was seen in the treatment group as soon as 4 wk post first injection. By week 24 treated eyes had a mean improvement of 17 letters compared to a loss of 4 letters in the sham group. BCVA improved steadily from week 4 to week 24 in the treatment group. A sub-group analysis of perfused and non-perfused eyes showed a significant better VA improvement in both groups in the treated eyes.

Reduction in CRT was noticed even after 4 wk with a 457 μm reduction in the treatment group compared to a 144 μm reduction in the sham group. Reduction in CRT was significantly better in treated eyes both in perfused and non-perfused sub-groups.

No progression to NV was seen in the treatment group compared to 6.8% in the sham group. Regarding nonperfusion, at week 12 the proportion was similar whereas at week 24 there was much less non-perfused eyes in the treatment group.

The 1-year results of the COPERNICUS trial[113] were similar. Patients were treated with 2 mg aflibercept as needed (PRN). At week 52, 55.3% of the primary treated group gained ≥ 15 letters in VA compared to only 30.1% in the primary sham group. The mean VA gain was 16.2 letters *vs* 3.8 letters in both groups. No adverse events were noted in the second treatment period.

The improvement in VA was significant in both perfused and non-perfused eyes compared to the sham group even after PRN treatment. Regarding CRT the reduction observed at week 24 in the treatment group was maintained in the PRN regiment. The sham treatment group showed great reduction in CRT during weeks 24-52 and in the end of the 1 year study both groups showed a similar reduction of CRT, around 400 μm.

During a second year follow-up on the COPERNICUS patients VA continued to be superior in the primary treatment group, but CRT reduction which was similar at week 52, continued to be similar at week 100 with a mean of 3 injections for both groups[114].

Another phase 3 randomized, double-masked, multicenter clinical study of aflibercept for CRVO, conducted in Europe, is the GALILEO[89]. The randomization was 3:2 to monthly intravitreal 2 mg aflibercept injections *vs* sham injections.

Results were similar to COPERNICUS with VA improvement of ≥ 15 letters at 6 mo 60.2% in the treatment group compared to 22.1% in the sham group. The mean change was 18 letters compared to 3.3. An important note is that the change between the treatment and sham groups was greater among patients with disease duration of up to 2 mo. The proportion of patients reaching the 15 letter gain endpoint at 6 mo among the treatment group was 70.9% among patients with disease duration of fewer than 2 mo and 50% in patients with disease duration of over 2 mo.

The anatomical outcome was also similar to that of the COPERNICUS with a different of 279 μm between treatment group and sham group in the CRT reduction. No significant ocular or non-ocular adverse events were noticed.

In the second year of the GALILEO study[115] the treatment group continued the 2 mg aflibercept treatment PRN and the sham group continued receiving sham injections. After 52 wk the percentage of patients with at least 15 letters VA improvement was 60.2% in the treatment group compared to 32.4% in the sham group. The VA improvement was of 16.9 letters compared to 3.8 letters and CRT reduction was of 423 μm compared to 219 μm in the sham group. The average in the PRN treatment was 2.5 injections during the second 6 mo.

The drug was found to be safe with no difference found in ocular and non-ocular adverse events between the two groups. Aflibercept is approved both by the FDA and EU for the treatment of ME secondary to CRVO.

Follow-up after the recommended treatment in the initial 6 mo as seen in the above mentioned studies is dependent on the treatment which was initiated for ME (corticosteroids or anti-VEGF). Follow-up is usually advised for up to 2 years, even in cases with no sight-threatening complications. Close monitoring should be held especially to detect conversion to ischemic CRVO and the occurrence or reoccurrence of ME. Development of collaterals of the optic disk or resolution of ME should bring the physician to lower the frequency of follow-up[15].

The recurrence or a persistent ME, diagnosed by means of decreased VA, biomicroscopy and OCT examination, should lead the physician to a decision to reinject. The use of laser photocoagulation is to be suggested for several populations such as non-responders or partially responders, or patients who are non-compliant with multiple injections.

Ischemic CRVO is characterized by a peripheral area

of non perfusion, initially defined in the CVOS Study, as greater than 10 disk diameters, as evaluated by FA, but more recently to a more extensive area as used in the ischemic index method, with the use of wide field retinal imaging[116].

In patients with ischemic CRVO, physician should primarily evaluate and asses both peripheral area of non perfusion and macular perfusion, the presence of ME and the existence of NV.

In a patient with ME, with FA that shows a relatively good perfusion to the macular area, treatment should be as outlined above as for non-ischemic CRVO. In cases where the macula is not perfused, the VA prognosis is very poor, yet immediate treatment with dexamethasone implants is reported to be effective.

In patients with a large non perfusion area, defined as more than 10 disc areas, an early and immediate PRP treatment is strongly suggested as an attempt to prevent the development of ocular NV, associated simultaneously with anti-VEGF intra vitreous injection[7].

In cases with less severe non perfusion, without any neovascularization (including on gonioscopy), scatter laser treatment aimed at the non perfused area may suffice with a very close monitoring and follow-up. Patients who pose a great difficulty to treat are noncompliant patients[31].

Patients with ischemic CRVO and (moderate) area of peripheral ischemia, and no ME nor NV should still be monitored monthly with a VA check, biomicroscopy, OCT and FA. In addition, the iris and corneal angle should be assessed regularly with gonioscopy[29].

Evidence nowadays supports the immediate PRP whenever an anterior segment NV (iris or angle) is found. An anterior segment NV which necessitates treatment is any degree of angle NV and/or iris NV in an area of 2 clock hours[7].

The complete PRP treatment can be carried out in one session or be divided into several sessions. The aim is to treat the retina completely from the periphery to the main vascular arcades. Typically the treatment in done on a slit lamp and consists of 1500-2000 burns (but usually more to 3000), 500 micron each, 0.1 seconds burn, and the space between burns should be 1 burn width. The burns should be in an energy level enough to produce a white burn in the retinal layers. PRP should begin in the inferior quadrants with avoidance of areas with retinal hemorrhages. Repeating treatment can be done whenever anterior segment NV does not regress. Today with the NAVILAS and PASCAL a great degree of accuracy is seen with lesser variations between burn size and a more uniform burn shape[117].

A treatment combination of PRP and anti-VEGF injection has not been tried in a randomized clinical trial, but has been suggested with favourable results in some publications and seems reasonable to attempt, in order to achieve faster regression of anterior segment NV and/or at least limit the evolution, hemorrhage and pain associated to NVG along with IOP reduction[68,118,119]. No indication in the studies mentioned about the timing of bevacizumab injection related to the PRP. Since those were all retrospective studies, the decision regarding timing is reserved to the physician as suited to each patient.

Posterior segment NV of the retina or disc can appear alone or along with anterior segment NV and needs to be actively detected during monitoring due to the risk of vitreous hemorrhages. In cases of posterior segment NV an immediate and non delayed PRP treatment is in order.

Anti-VEGF mono-therapy can only lead to a transient regression of NV[118,119]. No clinical data is available about the efficacy of anti-VEGF mono-therapy to stop NV, but repeated injections may be required to stop NV progression, probably without complete cessation.

A PRP treatment in conjunction with anti-VEGF may prove to be more effective even if still not tried in controlled studies.

In cases of severe NV, especially with vitreous hemorrhage, early PRP is strongly indicated (in all areas accessible). In these cases anti-VEGF injection may help in controlling the development of NV until the resolution of the vitreous hemorrhage allowing better visualization for complete PRP treatment.

In patients with neovascular glaucoma, the intravitreal injection of anti VEGF has been shown regress iris NV and improve the level of obstruction of the angle[120]. Some case series has shown that anti VEGF (Bevacizumab) with PRP induced a faster regression of iris NV than PRP alone[68].

Juvenile CRVO, defined as CRVO in patients under the age of 50, should be differentiated from the traditional CRVO because of a different pathogenesis and clinical course. In some patients the CRVO is related to a systemic disease and patients should be evaluated with a complete systemic workup for the underlying cause.

Juvenile CRVO could often present as benign, well perfused, with limited or no risk factors. Sometimes Juvenile CRVO could be preceded by inflammation as evident by cells in the vitreous[50]. The visual prognosis is usually better than the traditional CRVO, though the risk of complication may become the same, after one or more recurrence.

There is evidence showing that steroids treatment in a systemic administration can hasten the resolution of symptoms. It is custom to treat such patients that have ME with intraocular steroids, especially Ozurdex though little evidence exist.

Strategy of treatment

The randomized controlled studies on RVO have provided much information regarding treatment. An important lesson from those studies is that the duration of the disease before initiation of treatment is an important factor influencing outcome. Treatment is beneficial in any stage of the disease, including in the late stages. It has been shown that in patients with a shorter duration of the disease, the rapid initiation of treatment may be more beneficial and the outcome is better.

Patients with CRVO should be first screened for known risk factors and in case any, the family physician should be notified regarding the disease. The manage-

ment and control of the risk factors mentioned earlier should be fast and aggressive. The patient is evaluated by VA assessment, biomicroscopy, measurements of intra ocular pressure, and OCT. Examining the patient with fluorescein angiography should be done in order to evaluate areas of ischemia in the periphery and the macular area. FA can also evaluate for the existence of ME or NV of the disk or retina. NV of iris or angle should be determined in a gonioscopy examination. Distinguishing the subtype of CRVO should be done according to the extent of ischemia as seen on FA.

In cases of preserved VA of 20/40 and better, observation in a monthly fashion is advised, at least for the first 3 mo. If no sight-threatening complications are detected, the follow-up may be continued every other month for at least 1 year. All follow-up visits should include VA assessment, OCT and biomicroscopy and FA when needed.

In cases of decreased VA of less than 20/40, the physician should assess for the presence of ME. In the presence of ME, treatment should be initiated promptly. First line treatment should be with a properly approved drug, with Ozurdex and re-treatment decision based on the follow-up, or with injections of an anti-VEGF drug every month for 3-6 mo, with additional injections based on the progression of ME. As for BRVO, same considerations should be taken to account in deciding the first line treatment.

In cases of nonperfused CRVO, in the presence of ME, treatment is still warranted, but the prognosis is poor. First line treatment should be with a properly approved drug, with Ozurdex and re-treatment decision based on the follow-up, or with injections of an anti-VEGF drug every month for 3-6 mo, with additional injections based on the progression of ME. The addition of PRP treatment directed at areas of non-perfusion should also be considered by the physician in order to prevent NV. In cases of macular ischemia the prognosis for VA improvement is generally poor even in cases of prompt treatment and ME resolution. As mentioned before, same considerations should be taken in deciding the first line treatment.

At any visit during follow-up, the identification of neovascularization anywhere in the posterior or anterior chamber should prompt the treatment with scatter laser photocoagulation to the ischemic areas, guided by FA. The addition of an intravitreal drug, steroids or anti-VEGF should be considered, although not proven in the trials available.

GENERAL ASPECTS OF MEDICAL TREATMENT

The treatment of RVO patients has a long course. Multiple visits with examinations and intravitreal injections are the main course of action today. The common use of intravitreal injections is a burden on the patient and may cause further morbidity.

When treating patients with Ozurdex, a close monitoring should be advised and a reinjection should be done in cases of VA deterioration due to recurrence of ME usually after 5-6 mo.

When treating with anti-VEGF treatments, usually initiating treatment with Ranibizumab or Bevacizumab, two main methods can be employed. The first method is the monthly injection of anti-VEGF for the first 3 mo followed by a PRN approach. The patient is examined every month for the first 6 mo followed by an exam every other month for the rest of the first year. Injection is carried out only if recurrence is noted by VA worsening and ME presence on OCT.

The second method is rising among practitioners and is the treat and extend. After the primary 3 injections the patient is being injected in every visit until macula is dry. Since achieving a dry macula, the patient is evaluated by VA exam, biomicroscopy and OCT and is being injected in every visit. If macula is considered dry in the examination, the follow-up time increases by 2 wk and so on after every visit with no ME. If ME is presence in one of the visits, the follow-up decreases by 2 wk. This method allows the practitioner to discover the precise amount of time between injections for the individual patient with close enough monitoring and less injections than other methods.

In a review of intravitreal therapy for ME secondary to RVO, all anti-VEGF treatments showed a better improvement in VA than steroid treatment at month 12. The greatest gain in VA in CRVO patients after 12 mo was shown with the use of aflibercept and Bevacizumab with a gain of 16 letters compared to Ranibizumab with 14 letters improvement. In BRVO patients Ranibizumab showed to bring the greatest gain of 18.3 letters compared to Bevacizumab with 15 letter gain[121].

The use of longer-acting dexamethasone implant (Ozurdex) in conjunction with anti-VEGF therapy was examined in a small prospective, non comparative trial. VA gains were achieved up to 6 mo 14 letters, with 29% showing a $\geqslant$ 15 letters gain. CMT decreased by 200 μm. The mean time to re-treatment was 125.9 d, but it was unnecessary in 18.6% of patients[122]. The study demonstrated the synergy between both drugs with increasing VA and prolonging time between injections compared to each drug alone.

A recent prospective study on the effects of multiple anti-VEGF injections on IOP resulted in the conclusion that multiple injections were not found to be a risk factor for elevation in intra ocular pressure[123].

SURGICAL APPROACHES IN RVO TREATMENT

Few surgical approaches are utilized today in the treatment of RVO. These treatments target the vein occlusion itself or the macular edema. Most surgical treatments are abandoned and not in use nowadays due to the new and

effective pharmacological treatments.

Radial optic neurotomy

Radial optic neurotomy (RON) was used in the past for the treatment of CRVO[124]. However the benefit effect has not been studied enough and is still questionable[125]. In most places this technique is not used.

The surgical approach relied on the assumption that the radial incision will decompress the pressure on the vein.

Optic neuropathy leads to the development of optociliary venous anastamosis (or retino-choroidal shunts), which increase the retinal venous outflow[126-130]. Incisions are made on the nasal side of the optic nerve, radial to the optic nerve itself and parallel to the nerve fiber layer. A study conducted on 11 CRVO patients, 73% had improved vision with an average gain of 5 lines.

Hayreh[125] raised the concerns about the location of the incision close to the central retinal artery which can cause optic nerve head ischemia and complete vision loss. RON was associated with some serious complications in more than 71% including damaging central retinal artery, central retinal vein, optic nerve fiber, globe perforation, retinal detachment, cataract, choroidal neovascularization and anterior segment neovascularization[124,130,131].

Patient selection is important with more benefit for patients with CRVO of under 90 d and a pronounced peripapillary swelling[127].

RON is a very questionable procedure with controversial benefits and serious possible adverse events. Nowadays it is generally abandoned except for selected cases.

Chorioretinal venous anastamosis

In this procedure, in order to bypass the occluded vein, a shunt is made between a retinal vein and the choroid. This procedure creates another route to for the retinal outflow and relieves the obstruction. The anastamosis can be induced by laser or surgery[132-134].

A successful anastamosis was first reported in 33% with various degrees of VA improvement[132]. However complications were described in several studies and included posterior vitreous detachment, hemorrhages, retinal fibrosis, NV of the choroid, retinal ischemia and retinal detachment[129,132,134].

The anastamosis, in all the techniques, does not reperfuse areas of nonperfusion, however it leads to better perfusion of the perifoveal and parafoveal areas, reduce ischemia, increase venous return, decrease macular edema and improve VA.

This technique also is generally abandoned and not in use.

Pars plana vitrectomy

Pars plana vitrectomy (PPV) with ILM peeling can bring resolution of retinal damage and ME in CRVO patients[135-137]. The exact mechanism is unknown but 70% of RVO patients have shown decreases retinal thickness and increased VA after this operation[136,137], with an effect of up to 5 years[138].

This procedure is reserved to patients where other treatments, especially intravitreal injection have failed in achieving improvement, and the blood perfusion of the macula is sufficient to allows improvement of VA[136,139-146].

Successful results after PPV without ILM peeling have been described. PPV itself removes VEGF and other mediators from the vitreous and allows better oxygenation of the retina[147]. PPV with gas/air tamponade for ME showed a statistically significant improvement in BRVO patients[148,149]. In CRVO patients the benefit is questionable[150]. This procedure can also be combined with intravitreal injection of steroids which permits a more rapid and lasting action.

PPV is hardly used in most clinics for the purpose of RVO treatment.

Injection of t-PA through retinal vein cannulation

A need for direct tissue type plasminogen activator (t-PA) injection had followed some unsuccessful attempts to treat RVO patients with t-PA systemically or intravitrealy[151]. The surgery includes PPV with removal of the posterior hyaloid, and injection of 200 μg/mL t-PA to the optic nerve head through a cannulation of a peripapillary retinal vein.

This technique is favourable because: (1) t-PA is delivered directly to the site; (2) Allows the visualization of the drug reaching the thrombus; (3) Very small dose provides sufficient concentration near the thrombus; and (4) The injection can dislodge the thrombus and induce dilatation of the central retinal vein. VA was increased in about 50% of the CRVO patients. However in another study the results were poor with high complication rate[152].

This technique can cause some complications like vitreous hemorrhage, retinal tears or detachment, NVG formation, endophthalmitis and phthisis bulbi. Only retrospective data is at hand. This technique is also hardly ever used.

Arteriovenous sheathotomy

The surgical procedure, first introduces in 1988, included PPV with posterior hyaloids detachment and the opening of the adventitial sheath at the location of the arteriovenous block in BRVO patients and resulted in improved visual acuity[153]. The endpoint was the separation of arteriole from the venule. More recently, better results were seen using a bimanual technique followed by intravitreal recombinant t-PA[13].

Most studies regarding this surgical procedure failed to show an outcome justifying the risk of the surgery in BRVO patients[127,154]. In a study comparing this technique with intravitreal triamcinolone acetonide in BRVO patients, authors showed similar anatomical and functional improvement after 6 mo[155].

A recent match-control study compared 45 eyes with BRVO who underwent arteriovenous sheathotomy to 45 naïve eyes with BRVO. Improvement in VA was 0.42 logMAR in the treatment group compared to 0.22 logMAR in the control group. The mean postoperative CMT was

significantly thinner than the control group at 1 mo, but not at 3, 6 and 12 mo[156]. This technique is not actually utilized in most clinics.

Endovascular cannulation with a microneedle

This is a new surgical treatment in which a retinal endovascular cannulation using a microneedle is done in eyes with CRVO, in order to flush the thrombus out of the central retinal vein and through the lamina cribrosa. Seventy-five percent of patients had a VA improvement of 15 letters or more 24 wk post surgery, mean BCVA improved by 16.3 letters and CFT decreased by 271 μm. No adverse events were noted[157].

This technique is not actually utilized in most clinics.

PREVENTION

The prevention of recurrent RVO in the same eye, or fellow eye involvement has been discussed in several studies without any benefit shown, including in the use of anti-aggregates or anticoagulants[54,158].

The only available data about recurrence supports the medical treatment of underlying cardiovascular and other systemic and ocular risk factors as mentioned above.

BURDON OF RVO

Studies estimate that there are about 500 new RVO patients per million population[38], which can be divided to 85% BRVO and 15% CRVO.

Despite the large numbers, only 40%-50% require intervention, as the others have good vision not necessitating ophthalmological intervention[7,38].

CONCLUSION

RVO is a common disease and responsible for a large percentage of ocular morbidity and decreased vision. The modern imaging techniques allow fast diagnosis with detection of the ischemic forms if presence, and the complications, mainly macular edema with OCT and neovascularisation with biomicroscopy and gonioscopy. Studies have shown that fast diagnosis and treatment initiation brings better outcome in terms of visual acuity.

The treatment modalities have evolved over the last few years with the introduction of Ozurdex, anti-VEGF treatments including bevacizumab and ranibizumab and the new and promising aflibercept. The diversity allows the physician to switch between drugs according to patients characteristics and reaction to treatment. The recent extension studies for the large trials suggest benefit of both CS and anti-VEGF treatment after 36-48 mo. The ongoing COMO study will shed more light on the first choice for treatment in the comparison between Ozurdex and ranibizumab.

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REVIEW

What is new in central serous chorioretinopathy?

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Abstract

Central serous chorioretinopathy (CSCR) is considered a benign, self-limiting disease. However, as many as third of the patients have recurrent episodes or chronic disease that may cause significant functional impairment. New diagnostic tools and new treatment modalities are emerging in order to improve the functional outcomes of these patients. Spectral domain optical coherence tomography (SD-OCT) has the ability to image individual layers of the retina and choroid. SD-OCT images in CSCR patients have demonstrated increased subfoveal thickness measurements, high reflective deposits in areas of subretinal precipitates and changes in the Retinal pigment epithelium layers of the asymptomatic eyes of patients with supposedly unilateral CSCR. A positive correlation was found between the level of distribution to the layer of inner segment/outer segment junction of the photoreceptors and the visual impairment. Fundus autoflouresence images show a wide variety during different stages of the disease in CSCR patients. Minimal abnormalities during the early stages are followed by hyperautofluoresence in the detached area in later stages, often in a manner of inferior gravitation and at the borders of the detachments. The chronic phase is characterized by varying degrees of atrophy and areas of decreased autofluorescence surrounding areas of chronic leaks. These changes help differentiate an active disease from an inactive state. Multifocal electroretinography (mfERG) has the ability to demonstrate a persistent depression despite the resolution of subretinal detachments. It is therefore being investigated as a follow up tool for patients with chronic CSCR. An excellent correlation was found between changes in mfERG and visual function. Macular microperimetry, measuring retinal sensitivity within the central visual field, is intended to compensate for the underestimation of visual impairment in patients with macular diseases. Reduced retinal sensitivity was found in areas of previous subretinal fluids in CSCR patients. The device can also serve as a follow up tool in these patients. Regarding treatment in CSCR patients, focal argon laser photocoagulation treatment may be applied to small extrafoveal leaks. However, the main purpose of this treatment is to shorten disease duration, with no advantage over observation regarding final visual outcome, rate of progression to chronic CSCR or number of recurrences. Photodynamic therapy (PDT) with verteporfin has been shown to completely resolve serous detachment in 60%-80% of patients and to have a partial affect in the remaining patients. Reduced-fluence treatment is replacing full-fluence therapy in order to minimize side effects with no accompanying reduced effectiveness. Visual acuity is also improved following reduced-fluence PDT compared to placebo. It has also been found that patients with intense hyperfluorescence are more likely to show resolution of accumulating fluid compared to patients with mild or no leakage observed on indocyanine-green angiography prior to treatment. Regarding newer treatment modalities, intravitreal injections of anti-vascular endothelial growth factor agents have a limited effect in patients with CSCR. Recent reports have not demonstrated an advantage for this treatment in regards to anatomic and functional outcome. Micropulse diode laser was not proven to be safer or more effective than argon laser or PDT. Corticosteroid antagonists, not tested in controlled trials, may have a beneficial effect in patients with CSCR. Aspirin may also play a role in treating these patients, with rapid recovery of visual acuity and reduced number of recurrences observed. In

conclusion, imaging is evolving rapidly while the clinical implications of these new imaging modalities are less clear. Large randomized trials investigating different treatment modalities are still lacking.

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Key words: Central serous chorioretinopathy; Optical coherence tomography; Fundus autoflouresence; Multifocal electroretinography; Macular microperimetry

Core tip: (1) New diagnostic tools and therapies may improve the prognosis of patients with chronic or recurrent central serous chorioretinopathy; (2) Changes in fundus autoflouresence images help differentiate an active disease from an inactive state; (3) Multifocal electroretinography and macular microperimetry may serve as follow up tools due to their ability to measure macular visual function; (4) Focal argon laser photocoagulation shortens disease duration but does not affect final prognosis; (5) Reduced-fluence photodynamic therapy improves visual acuity and resolves serous detachments; and (6) The role of anti-vascular endothelial growth factor agents, micropulse diode laser, corticosteroid antagonists, aspirin, anti-viral or Helicobacter pylori treatment is still being investigated.

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INTRODUCTION

Central serous chorioretinopathy (CSCR) was first described by Albrecht von Graefe in 1866 as a relapsing central luetic retinitis[1]. The various terms later used to describe the disease, including the current acceptable term CSCR first used by Gass[2] in 1967, have omitted the relapsing characteristic from the term. However, relapsing serous detachments of the neurosensory retina are known to occur in as many as third of the patients[3]. Moreover, the recurrent and chronic nature of CSCR may result in severe and irreversible visual loss in these patients[4]. Therefore, in order to improve patients outcome, there is an ongoing search for new diagnostic tools, shedding more light on disease pathophysiology, and for new treatments and different treatment protocols.

PATHOPHYSIOLOGY

The typical presentation of CSCR is serous detachment of the neurosensory retina, but the source of the accumulating subretinal fluid is still not completely understood[2-13]. Retinal pigment epithelium (RPE) dysfunction has been hypothesized as the primary pathologic mechanism in CSCR, in part due to images obtained using fluorescein angiography (FA)[4-6]. These images show characteristic single or multiple leaks from the RPE, implicating the RPE as a major factor in the pathophysiology, as can be seen in Figure 1. However, different investigative tools led investigators to challenge this hypothesis. According to some reports, the choroid seems to be primarily affected, with the retinal changes seen with FA representing a later stage in the mechanism of the disease progression[7].

In order to further understand the role of the choroid in the disease, indocyanine-green angiography (ICGA) images were investigated. The congestion and dilatation of choroidal capillaries and veins, the choroidal staining and the leakage into the interstitial space all prove the choroid plays a major role in the accumulation of fluid in CSCR[12,13]. These changes in ICGA images are demonstrated in Figure 2. However, ICGA was found to have some limitations as a tool for diagnosis and follow up of patients. Previous studies on cross-sectional optical coherence tomography (OCT) images of eyes with chronic CSCR reported increased choroidal thickness observed, with no corresponding hyperflouresence observed on ICGA[14]. Moreover, ICGA gives a 2-dimensional scans, which means that all choroidal layers overlap in the angiogram.

NEW INSIGHTS ON PATHOPHYSIOLOGY FROM NEW IMAGING AND EXAMINATION MODALITIES

Spectral domain optical coherence tomography

The introduction of spectral domain optical coherence tomography (SD-OCT) as a more accurate imaging tool, with its ability to characterize individual layers of the retina and choroid and its noninvasive characteristic, has led to important observations regarding CSCR. The subfoveal thickness was found to be increased by 50%-80% in CSCR patients compared to normal eyes in different reports, when measured by enhanced depth imaging OCT[14-17].

Another measurement that can be performed with SD-OCT is the thickness of the outer nuclear layer (ONL). In one study, ONL thickness was found to be correlated with visual acuity in patients with resolving CSCR[18]. In that study, the mean ONL thickness measured in patients with resolved CSC was 74.6 μm in patients with visual acuity worse than 20/20 compared to 103 μm in patients with visual acuity of 20/20 or better[18]. That same group of researchers also showed elongation of photoreceptors outer segments and decreased thickness of the outer nuclear layer in CSCR, as a possible sign for photoreceptors apoptosis[19].

SD-OCT has also shed some light on the multiple, dot-like, yellow precipitates and subretinal yellow material within the area of a serous retinal detachment in patients with CSCR. These deposits correlate with high reflective deposits on SD-OCT[20,21] (Figure 3). Different hypothesis regarding these substances has been proposed, including the accumulation of shed photoreceptor outer segments, fibrin or lipids, or macrophages clearing the subretinal

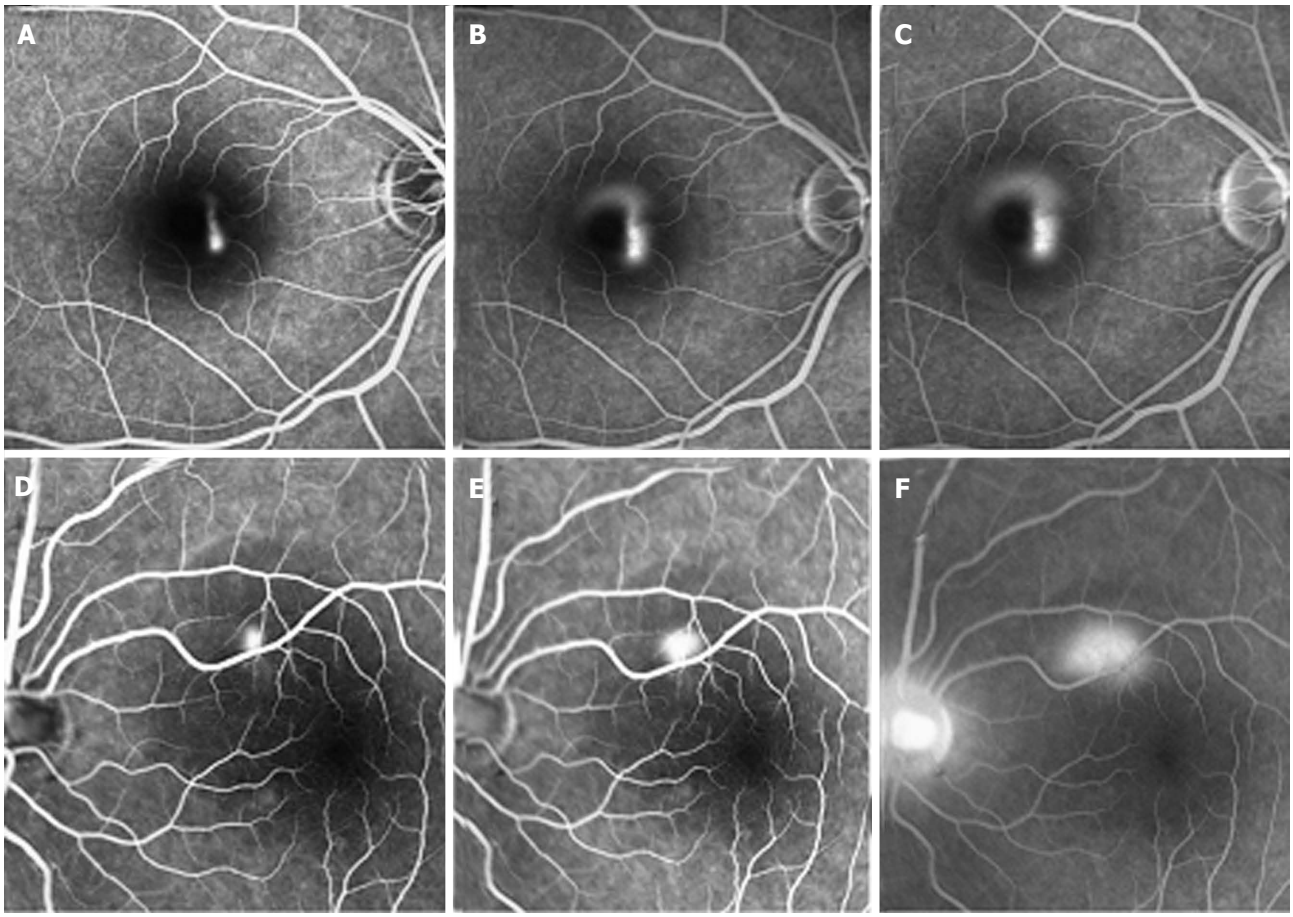

Figure 1 Two different patterns of hyperfluorescent dye leakage on fluorescein angiogram in acute central serous chorioretinopathy; Smokestack pattern of leakage (A, B and C) and inkblot pattern of dye leakage (D, E and F).

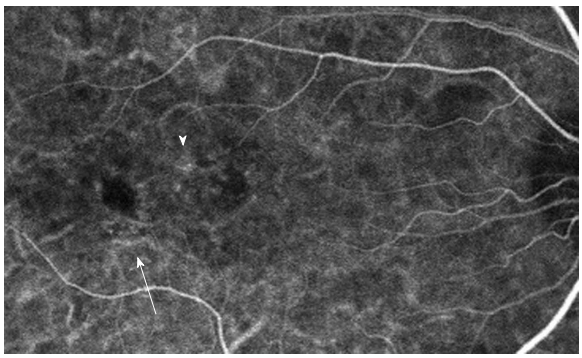

Figure 2 Indocyanine green angiography in a patient with chronic central serous chorioretinopathy. Note congestion and dilatation of choroidal capillaries and veins (arrow) and choroidal staining (arrowhead).

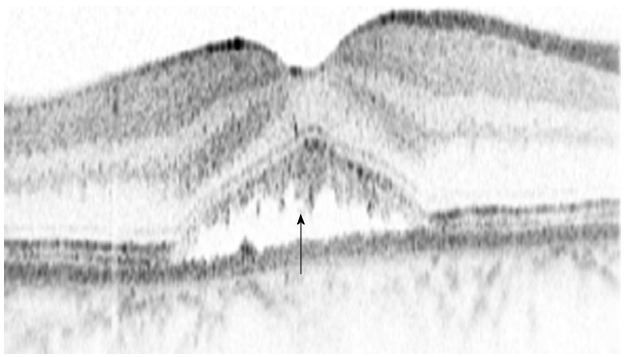

Figure 3 Spectral domain optical coherence tomography of acute central serous chorioretinopathy. Note high reflective subretinal deposits within the area of a serous retinal detachment (arrow).

space. However, the exact nature of these deposits and their origin is yet to be determined[21].

The bilateral nature of CSCR was also demonstrated by SD-OCT, even in eyes with supposedly unilateral disease[22]. Changes in the RPE cells layer has been previously shown in patients with CSCR, specifically around areas of a demonstrated leakage on FA[23]. This study investigated these RPE changes in the asymptomatic eyes of patients with CSCR in the other eye, using 3 dimensional single-layer RPE analyses. Presence of RPE bumps was observed in 94% of eyes and pigment epithelium detachment (PED) in 11.8% of eyes, compared to 8% of eyes with RPE bumps and no PED observed in normal control eyes[23].

Special attention has been addressed to the layer of inner segment/outer segment (IS/OS) junction in different retinal disorders. The level of disruption to this layer in different retinal disorders has an excellent correlation with visual acuity[24-27]. That correlation is also maintained in patients with CSCR[18,28-30]. The length of IS/OS dis-

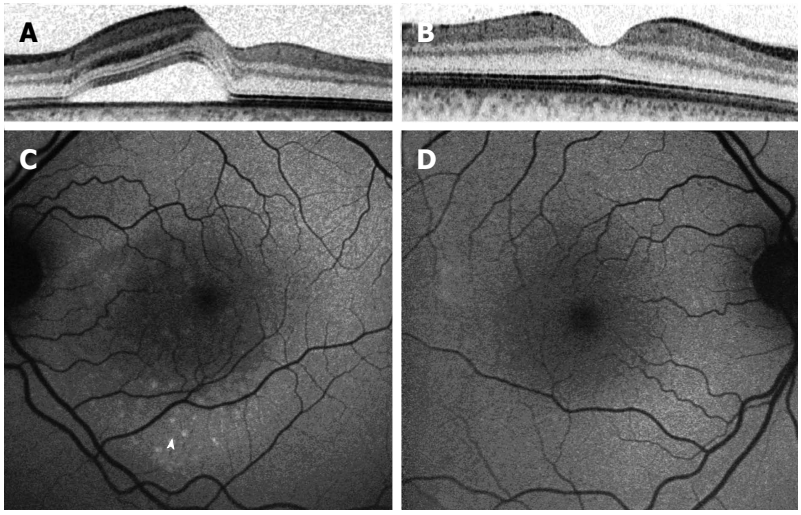

Figure 4 Imaging of a 38-year-old patient with central serous chorioretinopathy, one month following the beginning of his symptoms. Comparison of left (A) and right (B) eyes imaged with spectral domain optical coherence tomography shows a serous retinal detachment in his left eye. Minimal changes are seen with fundus autofluorescence imaging (C), consisting of a granular pattern of increased autofluorescence in the area of retinal detachment (arrowhead), compared to images of the right eye (D).

ruption, loss of foveal IS/OS and the level of integrity of the external limiting membrane layer were also found to be significantly correlated with visual acuity[31].

A newer generation of SD-OCT, swept-source OCT (SS-OCT), has also been investigated in patients with CSCR[32,33]. Ferrara *et al*[32] investigated the images of 15 eyes with chronic CSCR using SS-OCT. They documented PEDs in all eyes, as well as morphologic changes in the choroid underneath observed RPE changes and beyond these changes. They also observed focal and diffuse vascular dilation at the level of the choriocapillaris in half of the enrolled eyes, and at the level of Sattler's and Haller's layers in all eyes[32].

Fundus autoflouresence

Fundus autoflouresence (FAF) images were also shown to have an added value in the understanding of CSCR pathophysiology. Images of patients through different stages of the disease show a variety of autoflouresence phenomena, implying an ongoing damage to the RPE and photoreceptors. While Patients imaged within the first month following diagnosis have minimal abnormalities seen in their FAF photography (Figure 4), the next months are characterized by an increased hyperautofluorescent in the detached area of retina[34-36]. Some hyperautoflouresence appears as a granulated process, in correspondence to pinpoint subretinal precipitates[37]. The material often gravitates inferiorly or is shown to be collected in deposits at the border of the detachment[34]. These patterns are demonstrated in Figure 5. After resolution of subretinal fluid, the hyperautofluorescence of the fundus abates, suggesting that the accumulated material could be cleared with time. The chronic phase of the disease is characterized by varying degrees of atrophy, including areas of geographic atrophy and areas within fluid tracts descending inferiorly[34] (Figure 6). Areas of chronic leaks can have decreased autofluorescence surrounding them. These areas of hypoautofluorescence appear to expand in size with increasing chronicity of the disease[38]. In chronic CSCR eyes, inactive disease can be differentiated from an active disease by the lack of hyperautoflouresence, with only the atrophic component remaining as areas of hypo-autofluorescence[34] (Figure 7).

Multifocal electroretinography

The main advantage of multifocal electroretinography (mfERG) is the ability to demonstrate a persistent depression despite the resolution of the accumulating subretinal fluids. Hence, it has been investigated as a follow up tool for patients with chronic or recurrent CSCR as well as for examination of the seemingly healthy fellow eye[39]. It has been argued whether the pathologic findings in mfERG correspond with and are limited to the clinically observed areas of detachments or extend beyond these areas[39-41]. Excellent correlation was observed between changes in mfERG and function[42]. In a cross-sectional observational study by Lai and colleagues on 45 eyes with acute CSCR, it has been demonstrated that despite the fact that the outer retinal dysfunction is mostly localized to the central macula, a more widespread impairment in the more peripheral macula exists in the inner layers of the retina[43].

Macular microperimetry

Visual function evaluated only by the measurement of visual acuity may underestimate the level of impairment in patients with macular diseases[44-49]. Macular microperimetry was designed to detect more subtle defects in visual function in these patients by measuring retinal sensitivity within the central visual field[50,51]. The device can also serve as a follow up tool due to its image-registration facility. Reduced retinal sensitivity is observed in areas with previous subretinal fluids[28]. This reduced sensitivity also corresponds with RPE irregularities found on OCT[52].

NEW INSIGHTS ON TREATMENT MODALITIES FOR PATIENTS WITH CSCR

Acute CSCR is a self-limited disease in the majority of cases, with good final visual outcomes. The common management of acute CSCR still remains observation

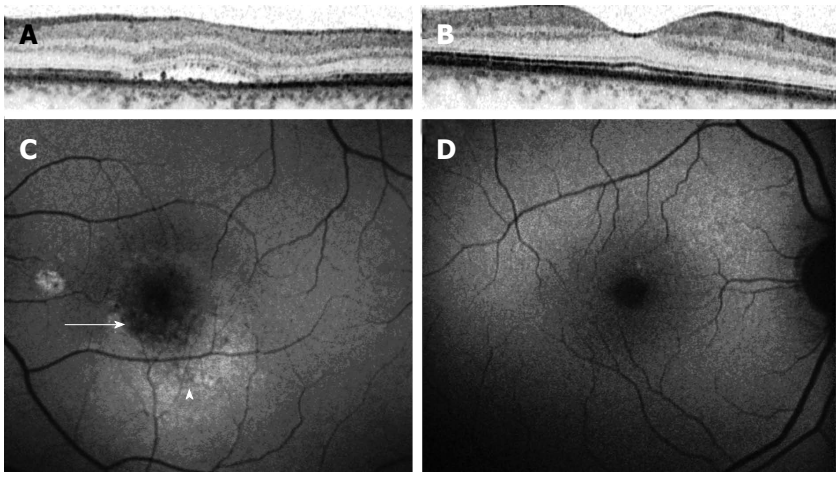

Figure 5 A 36-year-old patient with central serous chorioretinopathy, six months following the beginning of his symptoms. Comparison of left (A) and right (B) eyes imaged with spectral domain optical coherence tomography shows a serous retinal detachment in his left eye. In fundus autofluorescence imaging of the left eye (C) note the hyperautofluorescent in the detached area (arrow) beginning to form the manner of inferior gravitation (arrowhead), compared to images of the right eye (D).

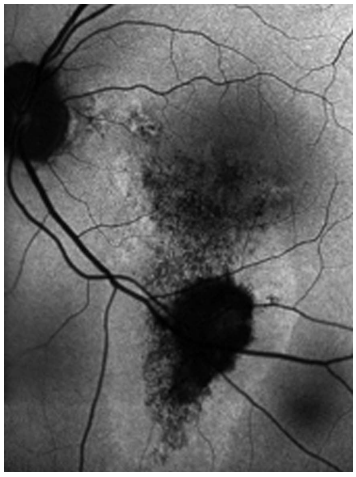

Figure 6 Fundus autofluorescence of a patient with chronic central serous chorioretinopathy showing inferior gravitational tracks and areas of decreased autofluorescence corresponding to areas of atrophy.

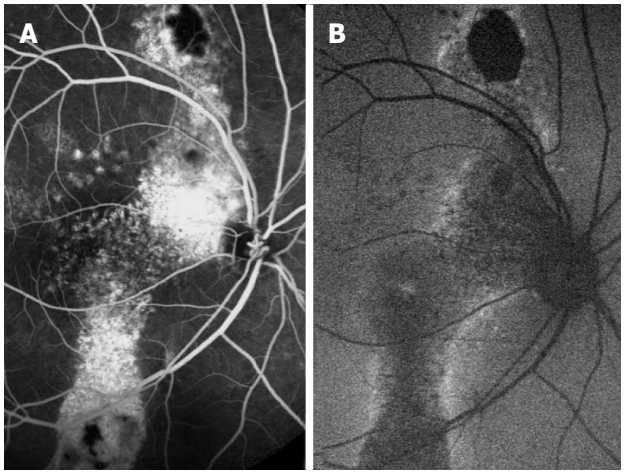

Figure 7 Chronic central serous chorioretinopathy; imaging from the same eye. Fluorescein angiography (A) with extensive hyperfluorescent areas, corresponding to areas of atrophy, seen as areas of decreased autofluorescence (B). Note the inferior gravitation pattern in both images.

and risk modification, with the exception of certain indications prompting immediate medical management. The common indications for the initiation of treatment are non-resolved subretinal fluid for 3 mo, decreased visual acuity from CSCR in the fellow eye or the need for immediate visual acuity rehabilitation. However, chronic CSCR as well as frequent recurrences of serous detachments may lead to RPE atrophy and other changes in the neurosensory retina leaving the patient with impairment of visual function[53]. Therefore, earlier treatment in selected patients may improve the final outcome and even prevent further damage.

Focal argon laser photocoagulation

Treatment with argon laser may be applied to small extrafoveal leaks on FA, mainly to shorten disease duration. Long term follow up results for argon laser treatment demonstrate no advantage over observation regarding final visual outcome, rate of progression to chronic CSCR or number of recurrences[54-56]. The main disadvantages of this treatment are the limited ability to affect final prognosis, the need for specific extrafoveal lesions to perform the procedure and possible side effects including the growth of new choroidal neovascularization (CNV)[56].

Photodynamic therapy with verteporfin

Standard dose photodynamic therapy (PDT) with injection of verteporfin has been shown to completely resolve serous detachment in 60%-80% of patients and to have a partial affect in the remaining patients[57-60]. However, serious side effects such as sudden visual loss, new CNV and atrophy of the RPE, had led to reduced-fluence treatment development[61,62].

Randomized and non-randomized trials on reduced-fluence PDT have found this treatment to be as effective as full-fluence therapy in regards to fluid resolution and functional outcome. Chan and colleagues performed a double masked randomized controlled trial on 63 eyes with acute CSCR treated with either half-dose PDT or placebo[63]. One year following treatment, approximately 95% of eyes in the PDT group compared to 58% in the placebo group had no subretinal fluid on OCT. Visual acuity at one year follow up was improved or stabilized in all patients in the PDT group compared to approximately 79% of patients in the placebo group[63]. Wu and

colleagues observed an improvement in mfERG in 24 eyes with acute CSCR, compared with 10 eyes in placebo group[64]. New imaging modalities, such as microperimetry, demonstrated the efficacy of PDT, beyond improvement in visual acuity[65-67].

There is still an ongoing search for the best way to reduce PDT dose, either by decreasing the laser therapy time, lowering the laser energy, altering the time interval between injections of verteporfin or lowering the dose of verteporfin. Zhao *et al*[68] conducted a research testing different doses of verteporfin for CSCR patients. Their conclusion was that 30% of the standard dose was optimal both for achieving fluid resolution and for avoiding adverse events[68].

In order to compare half-dose PDT to argon laser, Lim and colleagues prospectively assessed 26 eyes with CSCR[69]. Their results showed an earlier anatomic and functional resolution after treatment with half-dose PDT compared to laser. These differences, however, were no longer noted 3 mo following treatment[69].

Clinical response for this treatment has been linked to the level of hyperfluorescence observed on ICGA[70]. Patients with intense hyperfluorescence were more likely to show resolution of the serous detachment compared to patients with mild or no leaks observed on ICGA prior to treatment[70]. A recent report by Kim *et al*[71] evaluated the efficacy of half-dose PDT targeting the focal leakage point on FA for acute CSCR. In this retrospective trial, all 10 eyes treated in this manner had complete resolution of subretinal fluid compared to 27.3% of eyes receiving no treatment. These differences were minimized at 12 mo follow up; with 90% of PDT group and 63.6% of observation group showing no subretinal fluid. No differences were noted in final visual acuity or recurrence rates between the two groups[71]. Therefore, this treatment protocol may serve as a substitute for focal argon laser treatment for hastening absorption of subretinal fluid.

Other treatment modalities

Anti-vascular endothelial growth factor agents: Intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents have dramatically changed the anatomical and functional prognosis of patients with retinal and choroidal diseases[72-74]. However, in patients with CSCR, improvement in prognosis following injections is more questionable, and anti-VEGF agents are not considered first line treatment. Despite the fact that VEGF levels were not found to be elevated in the aqueous humor of eyes with CSCR, many uncontrolled studies reported favorable results for anti-VEGF agents[75-84]. The largest series to date published by Lim *et al*[75] included 40 eyes in a prospective interventional case series. In their study, following one or two injections, 82.5% of patients achieved resolution of subretinal fluid at 4 mo follow up. However, they only included patients with acute CSCR, known to have a better prognosis; with no comparison arm for this study, and a relatively short follow up period[75].

A recent prospective, randomized study by Bae and colleagues compared ranibizumab injections to low-fluence PDT in 16 eyes with chronic CSCR[85]. Their conclusion was that the effect of ranibizumab was not promising compared with that of low-fluence PDT, in terms of anatomic outcomes. An important observation was that 50% of eyes in the ranibizumab group accomplished complete resolution only after they underwent additional low-fluence PDT[85].

A meta-analysis, conducted by Chung *et al*[86], identified four clinical controlled studies evaluating the effects of intravitreal bevacizumab injection in CSCR. In their data analysis, no significant differences in BCVA or central macular thickness (CMT) were found at 6 mo after injection between the bevacizumab group and the observation group. Another important issue they raised was that no report assessed severe complications or side effects of these intravitreal injections in patients with CSCR[86].

Micropulse diode laser

The main advantage of diode laser over argon laser is deeper penetration, reaching the choroid, mainly implicated as the pathologic origin of the subretinal fluid[87]. That sets the theoretical basis for the trials investigating the role of this laser in CSCR, as an attractive replacement for focal argon laser treatment. Verma and colleagues conducted a small randomized trial comparing the results of these two types of lasers in patients with acute CSCR[88]. Despite the fact that visual acuity was better in the diode laser treatment group 4 wk following the procedure, this difference was no longer observed 4 wk later[88]. Micropulse diode laser is considered less damaging to the RPE and photoreceptors, by applying short multiple pulses of energy instead of continuous energy. However, unlike the argon laser, the micropulse diode laser is less widely available and does not cause retinal bleaching guiding the operator when to stop laser application. In addition, micropulse diode laser was not proven to be safer or more effective than argon laser or PDT, and still requires a focal leak as seen on FA to guide treatment[89]. Therefore, the role of this laser as a substitute for conventional laser is still questionable.

Corticosteroid antagonists

The basis for corticosteroid antagonists administration for CSCR is the association found between the development of the disease and endogenous hypercortisolism (Cushing's syndrome)[90]. The hypothesis is that if this association exists with other hypercortisolemic states, than blocking the effect of corticosteroids may play a role in treating CSCR[91]. That hypothesis is further supported by the elevated serum cortisol levels commonly found in patients with CSCR[92-94]. The proposed medications, including ketoconazole, mifepristone (RU486), finasteride, rifampin, and anti-adrenergics, have not been tested in randomized, controlled trials.

Ketoconazole, an adrenocorticoid agent, has been investigated by two groups for the treatment of CSCR. In a prospective, case control study, Golshahi and colleagues

treated 15 patients with new onset subretinal fluid with 200 mg of ketoconazole per day for 4 wk[95]. No statistically significant benefit was found for that dosage[95]. An increased dose of 600 mg per day for 4 wk was later adminstered by Meyerle *et al*[96]. The results of this prospective, uncontrolled pilot study on 5 patients with chronic CSCR showed reduced serum cortisol levels, stable visual acuity, and anatomic improvement at 8 wk. They suggested larger, controlled trials to test the efficiency of ketoconazole in CSC patients[96].

Nielsen and colleagues treated 16 chronic CSCR patients with mifepristone (RU486), an active anti-glucocorticosteroid and anti-progesterone agent[97]. Favorable response was seen, with seven subjects gaining five or more letters of vision and seven subjects with improved OCT findings. Despite the fact that treatment was well tolerated without serious adverse effects in these patients, main obstetric concerns regarding this drug still limit its use[97].

Anti-adrenic agents, proposed to cause reduction of the adrenergic drive induced by stress, were also investigated for the treatment of CSCR. In his monkey model for experimental CSCR, Yoshioka suggested that inhibition of adrenergic receptors, particularly alpha receptors, may be beneficial[98]. Later studies investigating beta-blocking agents have shown partial improvement in CSCR patients, with no difference found between selective and non-selective agents[99-102]. However, none of the studies were controlled or randomized, and significant systemic side effects further limit the use of these agents.

Aspirin

The hypothesis that hypercoagulability plays a role in the pathogenesis of CSCR was based on a previous work showing increased levels of plasminogen activator inhibitor in patients with CSCR, compared to controls[103,104]. Caccavale and colleagues treated 107 CSCR patients with 100 mg acetyl salicylic acid (aspirin) once daily for one month and then every other day for five months[105]. A rapid recovery of visual acuity was observed after the first week of therapy, with low recurrence rate[105].

Anti-bacterial and anti-viral therapy

The hypothesis that an inflammatory damaging process has a role in the pathogenesis of CSCR is based on the characteristic of the disease. The proceeding stress as well the recurrent episodes of the disease have led investigators to consider a viral or a bacterial etiology.

The most investigated infectious association to CSCR is between the disease and *Helicobacter pylori* (*H. pylori*) infection[106-110]. Some investigators have noted a beneficial effect for *H. pylori* treatment in patients with CSCR[111,112]. In a randomized, controlled trial, twenty-five *H. pylori*- infected acute CSCR patients were treated with an anti-*H. pylori* treatment; another twenty-five patients with the same clinical presentations served as the control[112]. Subretinal fluid reabsorption time was significantly reduced in the treatment group, with no beneficial effect observed for final visual acuity[112]. Larger studies to confirm the association between H. pylori and CSCR are warranted.

Regarding a viral etiology, no large studies to establish the association between CSCR and any virus were published. Rathschuler *et al*[113] reported two cases of acute CSCR immediately started with an antiviral therapy (Acycloguanosine), with immediate regression of symptoms accompanied by an anatomic resolution of the leakage and the detachment. Larger studies to confirm the association between *H. pylori* or a viral etiology and CSCR are warranted.

CONCLUSION

CSCR is a common cause of visual impairment, especially in the middle aged population. Despite the fact that most patients will have spontaneous recovery, those with recurrent episodes or chronic disease may remain with significant functional impairment. The exact pathophysiology leading to subretinal fluid accumulation remains undetermined, but it is probably a combination of choroidal and RPE pathology. While imaging is evolving rapidly, the clinical implications of all these new imaging modalities are less clear. Treatment is still a subject of dispute, regarding indications, proper initiation time and type of treatment for both acute and choronic CSCR. That is mainly due to the fact that large randomized trials are still lacking.

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MINIREVIEWS

Retinal emboli

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Abstract

Retinal emboli are opacities identified in retinal arterioles and are often incidental findings on ophthalmic examination. They are generally composed of cholesterol, platelet-fibrin, or calcium and are thought to arise from carotid arteries, coronary arteries, or cardiac valves. In the general population, the estimated prevalence is 0.2% to 1.3%, and the estimated incidence is 0.9% to 2.9%. The transient nature of retinal emboli likely explains the variations between and within these reported figures. The strongest risk factor for retinal emboli is smoking, which has been reported consistently across many studies. Other likely risk factors include older age, hypertension, male sex, total cholesterol, coronary artery disease, and history of coronary artery bypass grafting. The presence of multiple risk factors, as is common in many patients, confers a higher risk for retinal emboli. Several studies suggest that retinal emboli predict an increase in stroke-related, all-cause, and possibly cardiovascular mortality. Due to these sequelae, patients often undergo further workup, most commonly carotid ultrasonography. However, given the low prevalence of significant carotid disease in patients with retinal emboli, further workup, such as carotid ultrasound, should be reserved for those with risk factors for carotid disease. All patients would benefit from medical optimization and coordinated care with the primary care physician.

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Key words: Retinal emboli; Hollenhorst plaque; Stroke; Carotid disease; Cardiovascular disease

Core tip: Retinal emboli occur in up to 3% of the population and predict an increase in stroke-related, all-cause, and possibly cardiovascular mortality. The strongest risk factor for retinal emboli is smoking, which has been reported consistently across many studies. Other likely risk factors include older age, hypertension, male sex, total cholesterol, coronary artery disease, and history of coronary artery bypass grafting. Because many patients with retinal emboli have multiple co-morbidities, they would benefit from medical optimization and coordinated care with the primary care physician. Further workup, such as carotid ultrasound, should be reserved for those with risk factors for carotid disease.

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INTRODUCTION

As early as 1862, retinal emboli were identified as discrete opacities in retinal arterioles. Many more accounts of these emboli have since surfaced, including a large case series by Hollenhorst that identified an association with carotid disease[1]. He described 3 main constituents of retinal emboli - cholesterol, platelet-fibrin, and calcium – which have been confirmed in histopathology reports[2-5]. Cholesterol emboli are the most common and are characteristically bright orange-yellow, highly reflective, migrate frequently, and are thought to originate from ulcerated atherosclerotic lesions on cardiac valves or from aortic and carotid endothelium[1,6,7]. Coronary arteries may also

Table 1 Prevalence and basic demographic features of patients found to have retinal emboli in large population-based studies

Ref.	Prevalence	No of participants	% male	Average age	Ethnicity
Wong *et al*[18]	0.2%	15466	44%	63	Mixed (21% black, 79% white)
Hoki *et al*[15]	0.4%	5959	42%	55	Latino
Cheung *et al*[14]	0.6%	3265	52%	59	Asian Malays
Klein *et al*[16]	1.3%	4926	44%	62	White
Mitchell *et al*[17]	1.4%	3654	43%	66	White

be a source, supported by the observation that coronary angiography can liberate cholesterol emboli into retinal arterioles[8-10]. Another less common source is an atherosclerotic lesion in renal arteries[11]. Cholesterol emboli are generally asymptomatic because their thin, flat shape usually does not result in an occlusion[7,12]. Platelet-fibrin emboli are creamy-white, irregularly shaped, immobile, and are postulated to arise from mural thrombus formation in carotid or coronary arteries[1,4,6]. Lastly, an "extremely white," irregular embolus represents calcium likely originating from calcified cardiac valves[1,13]. Given these likely sources, retinal emboli are thought to be indicators of cerebrovascular and cardiovascular disease. The remainder of this review will thus focus on the incidence, risk factors, outcomes, and management of retinal emboli.

PREVALENCE AND INCIDENCE

Several studies in asymptomatic subjects in the general population have identified the prevalence and incidence of retinal emboli. Among 5 modern population-based studies (The Beaver Dam Eye Study, The Blue Mountains Eye Study, The Los Angeles Latino Eye Study, The Singapore Malay Eye Study, and The Atherosclerosis Risk in Communities and Cardiovascular Health Studies), the prevalence of retinal emboli has been reported to range from 0.2% to 1.3%[14-18]. The difference in the reported prevalence among these studies could possibly be explained by the variations in basic demographic characteristics between the study populations (Table 1).

Only 2 studies have reported the incidence of retinal emboli. The Blue Mountains Eye Study identified the 10-year incidence to be 2.9%[19], which is higher than the 1.4% prevalence reported in the same study group in their earlier study[17]. In the Beaver Dam Eye Study, the 5-year incidence was reported as 0.9%[16] and the 10-year incidence was calculated to be 1.5%[20], as compared to the 1.3% prevalence reported in the initial report[16].

Of the 3 different types of retinal emboli - cholesterol, platelet-fibrin, and calcium - the most common is cholesterol. An estimated 46%-80% of all retinal emboli are composed of cholesterol, followed by 6%-32% platelet-fibrin and 6%-16% calcific[14,17,19,21,22]. Since the majority of retinal emboli are of the mobile cholesterol type, it is not surprising then, that many studies report dynamic changes in the presence of retinal emboli on subsequent exams. Hollenhorst[1] reported such changes in 39% of his cases at a subsequent visit, Schwarcz *et al*[23] in 84% of cases, and The Blue Mountains Eye Study and The Beaver Dam Eye Study in 87%-90% of cases[16,19,20]. While the distal migration of emboli is the most commonly accepted theory, another proposed mechanism for the disappearance of these retinal emboli is through autophagy, in which the endothelium engulf the embolus and lead to its extravasation into perivascular spaces[24]. Whatever the mechanism, the transient nature of retinal emboli thus makes it difficult to identify their true prevalence and likely contributes to the variations between different studies and the apparent discrepancies between the incidence and prevalence even within the same study group.

RISK FACTORS

Given the likely sources of retinal emboli, it has been postulated that the risk factors for retinal emboli are similar to the risk factors for vascular disease. However, the definite risk factors for retinal emboli are difficult to assess due to the transient nature of retinal emboli, the presence of multiple co-morbidities, differing demographics across reported studies, and a survivor effect wherein subjects who may be at highest risk are not included in the cohort. Although there are some inconsistent results across the different studies (Table 2)[14-20,25], some generalizations can still be made. Smoking appears to be the strongest risk factor and has been consistently associated with the presence of retinal emboli in all studies reviewed here. Most of the traditional vascular risk factors appear to be significantly associated with retinal emboli with the exception of diabetes, which has fairly consistently been shown not to confer increased risk. Indeed, the incidental finding of retinal emboli has been reported in 0.9%-1.9% of patients who undergo screening for diabetic retinopathy[21,26], which is within the range of the prevalence and incidence of retinal emboli reported in the general population.

As is the case with patients afflicted by other vascular diseases, patients with retinal emboli often have multiple risk factors. The additive effect of multiple co-morbidities was demonstrated in The Blue Mountains Eye Study, which found that the presence of 2 or more risk factors conferred a greater risk of having retinal emboli as compared to none or 1 factor[27]. The combination of hypertension and current smoking conferred the highest risk of retinal emboli with an odds ratio of 6.0 in subjects under age 70[27]. Any 2 or more of hypertension, current smoking, history of vascular event, and history of vascular surgery also led to an increased risk with an odds ratio of 4.6[27].

OUTCOMES

The presence of retinal emboli may be a harbinger of future vascular events and has been associated with increased mortality. In a 7-year follow-up study of 208 patients by Hollenhorst[28] and Pfaffenbach *et al*[29], the

Table 2 Risk factors for retinal emboli

Probable risk factors	Unlikely risk factors	Insufficient data
Smoking (8/8)	History of angina (2/5)	Elevated pulse pressure (2/2)
History of coronary artery bypass graft (3/3)	History of myocardial infarction (2/5)	Known carotid artery plaque (2/2)
Hypertension (5/7)	Body mass index/obesity (1/7)	LDL cholesterol (1/1)
Older age (4/6)	Diabetes (1/7)	Mean arterial blood pressure (1/1)
Coronary artery disease (2/3)	Aspirin use (1/3)	Previous vascular surgery (1/1)
Serum fibrinogen (2/3)	History of stroke (0/6)	Serum lipoprotein (1/1)
Systolic blood pressure (3/5)	Diastolic blood pressure (0/4)	Congestive heart failure (0/1)
Male sex (3/6)	Alcohol use (0/3)	Hemoglobin A1C (0/1)
Total cholesterol (3/6)	Hematocrit (0/3)	Hormone replacement therapy (0/1)
	Platelet count (0/3)	Serum triglycerides (0/1)
		Carotid artery bypass surgery (0/2)
		Serum glucose (0/2)

The numbers in parentheses indicate the fraction of studies reviewed in this article that report a statistically significant association with retinal emboli. A potential risk factor was considered to have insufficient data if there were fewer than 3 studies investigating its relationship to retinal emboli.

all-cause mortality rates were 8% at 3 mo, 15% at 1 year, 29% at 3 years, and 54% at 7 years in patients with a median age of 64 years at initial embolus detection. The most common cause of death was coronary artery disease (42% of deaths), followed by stroke (10% of deaths), other atherosclerotic vascular disease (10% of deaths), and ruptured aortic aneurysm (8% of deaths). Savino *et al*[30] reported the overall mortality as 28% during a 9-year follow-up period, with the largest proportion of deaths similarly attributable to cardiovascular disease (46% of deaths). The next largest cause of death was stroke (29% of deaths), which corresponded to a 4 to 5-fold annual increased stroke-related mortality compared to an age and sex-matched population. Howard *et al*[31] reported a 2.3-fold increased risk of death and 12-fold risk of fatal stroke as compared to age and sex-matched controls during a 6-year follow-up period. The Beaver Dam Eye Study[20] similarly reported a 2.4-fold increased stroke-related mortality and no statistically significant association with ischemic heart disease.

To achieve greater statistical power, a study was performed pooling mortality data from The Blue Mountains Eye Study and The Beaver Dam Eye Study. When adjusted for age and sex, there was a mild increase in cardiovascular mortality (HR = 1.46, 95%CI: 1.03-2.06), a moderate increase in stroke-related mortality (HR = 2.33, 95%CI: 1.34-4.07), and a mild increase in all-cause mortality (HR = 1.52, 95%CI: 1.18-1.96)[32]. After adjusting for multiple systemic factors, such as body mass index, hypertension, diabetes, current smoking, total cholesterol, high-density lipoprotein cholesterol, history of stroke, history of angina, history of acute myocardial infarction, retinal emboli were still significantly associated with increased stroke-related mortality (HR = 2.02, 95%CI: 1.07-3.81) and all-cause mortality (HR = 1.34, 95%CI: 1.02-1.76), although at a lesser magnitude. The risk of cardiovascular mortality became statistically insignificant (HR = 1.18, 95%CI: 0.80-1.73). These findings suggest that the presence of retinal emboli may be an independent risk factor for all-cause and stroke-related mortality. In reality, most patients do tend to have multiple systemic risk factors, which further increases mortality risk.

While associated mortality has been published in many studies, less commonly reported are morbidities linked to the presence of retinal emboli. Due to significant impact of disabilities on quality of life, these morbidities should not be ignored. The most common morbidity is non-fatal cerebrovascular infarction. In a study of 70 men with asymptomatic retinal emboli seen at the Albuquerque Veterans Affairs Medical Center, Bruno[12] reported an 8.5% annual rate of non-fatal stroke, which corresponds to a 10-fold increased risk of cerebral infarction as compared to controls matched for age and vascular risk factors. More specialized brain imaging techniques like diffusion weighted imaging has allowed the detection of subclinical strokes, with a study by Helenius *et al*[33] reporting that 20% of patients whose sole presenting complaint was acute monocular vision loss were found to have brain infarcts on the ipsilateral side. Other morbidities reported by Pfaffenbach *et al*[29] include claudication (9% of patients), angina or abnormal electrocardiogram (7% of patients), transient ischemic attack (3% of patients), and amaurosis fugax (1% of patients). However, the lack of statistical analyses provided for these sequelae make it difficult to ascertain whether the presence of retinal emboli confers an increased risk for these phenomena or whether these are related to the patients' other comorbidities and underlying vascular disease.

Because of the increased stroke mortality and morbidity in patients with retinal emboli, carotid ultrasonography and angiography are sometimes performed. However, data reported in the literature vary widely, not only with regards to the prevalence of carotid disease, but also in the way results are reported and how "significant" disease is defined. Among studies that do not specify the degree of carotid stenosis, as low as 23% and as high as 95% of patients with retinal emboli are estimated to have some carotid disease[18,25,31,34]. Significant carotid artery stenosis defined as at least greater than 50% was present in 17%-22% of patients with asymptomatic retinal emboli[25,34,35]. Other studies that defined significant carotid stenosis as greater than 70% reported a prevalence of

9%-22% in asymptomatic patients[21,26,36]. Lastly, when significant stenosis was defined as greater than 75%, a prevalence of 20% was reported[22]. Despite stroke-related mortality being most commonly reported sequela of retinal emboli, it should be noted that carotid disease, especially high grade stenosis, is still only found in a minority of these patients.

It has been postulated that the presence of visual symptoms could be an indicator of carotid disease. Bunt[37] reported that 17% of asymptomatic patients, 73% of patients with amaurosis fugax, and 100% of those with focal visual loss had significant stenosis. Bakri *et al*[36] found that there was a significant difference in the proportion of symptomatic and asymptomatic patients (25% *vs* 9%) when stenosis was defined as > 69% but not when defined as > 40%. This study also suggests that asymptomatic patients with a carotid bruit are more likely to have carotid stenosis. These findings may seem intuitive, but are not replicated in all studies. For example, O'Donnell *et al*[22] reported a similar proportion of carotid disease in symptomatic (21%) and asymptomatic patients (18%).

Since most patients with asymptomatic retinal emboli do not have significant carotid disease, only a small proportion undergoes carotid endarterectomy. Hadley *et al*[21] reported that 25 of 190 patients with retinal emboli (13%) had significant stenosis between 70%-99%, and only 10 of these patients underwent ipsilateral carotid endarterectomy. By the end of the study period (up to 7 years of follow-up), 4 of these 10 in the surgical group had died, but none from a stroke. Of the 15 who did not have surgery, 5 died during the follow-up period, none from a stroke although one patient did experience a non-fatal stroke. In Bunt's study[37], 28% of patients with asymptomatic retinal emboli underwent carotid endarterectomy, and no patients in either the non-surgical group or any of the surgical groups developed any subsequent symptoms of vision loss or cerebral ischemia during an 18-mo follow-up period. Schwarcz *et al*[23] reported that whether patients underwent carotid endarterectomy or not, both groups experienced recurrent retinal emboli and subsequent transient ischemic attacks. These reports seem to suggest that perhaps carotid endarterectomy for these patients does not affect mortality. However, the effect on long-term outcomes is limited in these studies due to short follow-up, small sample sizes, lack of data on medical interventions that were provided concurrently to the surgical group, and lack of data on medical interventions done to the non-surgical group.

Other less commonly used workup for retinal emboli include transcranial Doppler and echocardiogram. The incidence of cardiac pathology, such as valvular disease and wall motion abnormalities, was reported in 8%-43%[26,27,35]. It is unknown how many of these patients underwent cardiac surgery as a result. Ultimately, it is estimated that up to 45% of patients will have no identifiable cause despite extensive evaluation[35], suggesting that maximal extensive workup is neither cost-effective nor informative.

MANAGEMENT

The increased morbidity and mortality rates suggest a need for additional interventions in patients found to have retinal emboli. Given the coexistence of multiple medical problems, the presence of retinal emboli may simply be a marker of their underlying metabolic and vascular disease. Medical therapy should be the mainstay of management and should emphasize risk factor modification, such as stricter blood pressure control, the initiation of cholesterol-lowering medication, counseling for smoking cessation, encouragement of weight loss, diabetes management, the initiation of antiplatelet therapy, and monitoring through carotid auscultation[15,16,21,26,27,36,38].

The current guidelines[39] for the use of carotid ultrasonography in asymptomatic patients list the following indications: suspected of having carotid disease; have a carotid bruit; have symptomatic coronary artery disease, peripheral arterial disease, or atherosclerotic aortic aneurysm; or have at least 2 associated risk factors (hypertension, hyperlipidemia, tobacco smoking, a family history of a 1st degree relative with manifestations of atherosclerosis before age 60, or family history of stroke). The routine screening of the general population is not recommended. It has been suggested that carotid ultrasonography should be offered to all patients with retinal emboli[40], but given the low prevalence of significant carotid disease in these patients, it may be more reasonable to reserve carotid ultrasonography for patients who meet the aforementioned indications. Other imaging modalities like echocardiogram and transcranial Doppler are low yield and have not been recommended in the literature.

The currently established indications[39] provide strongest evidence for the use of carotid endarterectomy in symptomatic patients with at least 70% stenosis on carotid ultrasound (or at least 50% on catheter angiography) with low or average surgical risk and low anticipated perioperative mortality; and asymptomatic patients with greater than 70% stenosis and low perioperative risk of stroke, myocardial infarction, or death. Ideally, surgery should be performed within 2 wk of the index event. Surgery in asymptomatic patients with retinal emboli who are subsequently found to have significant carotid stenosis is more controversial[41], since carotid endarterectomy is an invasive procedure that itself carries a significant risk of perioperative mortality and postoperative stroke[39,42,43]. As previously discussed, small studies of the short-term outcomes of carotid endarterectomy are not suggestive of a mortality benefit of surgical management. Therefore, this subset of patients may benefit from referral to a vascular surgeon, during which it should be carefully considered whether the benefits of stroke prevention would outweigh the perioperative risks, taking into account the patient's comorbidities, individual risk factors, life expectancy, and complication rates of the surgical center. Large, prospective, randomized, controlled studies addressing the effects of carotid endarterectomy in this unique patient population will determine the out-

comes of this proposed algorithm.

CONCLUSION

Retinal emboli occur in up to 3% of the general population, particularly in those with risk factors similar to that of other vascular diseases. As such, there is significant overlap in patients with retinal emboli and other metabolic and vascular conditions. Therefore, management should involve working with the primary care physician to maximally control the underlying comorbidities and risk factors, such as smoking cessation, control of blood pressure, and lowering of serum cholesterol.

Carotid ultrasound has a low-yield for detecting significant carotid disease in patients with retinal emboli, suggesting that it should not be done routinely in this population but instead reserved for those who meet an established indication. Those who would benefit most from surgery are patients with significant stenosis > 70% and symptoms of an impending cerebrovascular event, such as unilateral weakness, unilateral sensory loss, aphasia, sudden monocular vision loss, or homonymous hemianopsia. The subset of asymptomatic patients with significant stenosis should be referred to a vascular surgeon for consideration of the risks and benefits of this invasive procedure.

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MINIREVIEWS

Age-related macular degeneration treatment in the era of molecular medicine

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Abstract

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the developed world. The quality of life of both patients and families is impacted by this prevalent disease. Previously, macular degeneration had no known effective treatment. Today, vitamins for non-exudative AMD and intravitreal injection of medications for its exudative form are primary forms of current treatment. Modern advances in molecular science give rise to new possibilities of disease management. In the year 2003 the sequencing of the entire human genome was completed. Since that time, genes such as complement factor H, high-temperature requirement factor A1, and age-relateed maculopathy susceptibility 2 have been discovered and associated with a higher risk of AMD. A patient's genetic make-up may dictate the effectiveness of current or future therapeutic options. In addition, utilizing genetic data and incorporating it into new treatments (such as viral vectors) may lead to longer-lasting (or permanent) VEGF blockade and specific targeting of complement related genes. There have also been considerable advances in stem cell directed treatment of AMD. Retinal pigment epithelial (RPE) cells can be derived from human embryonic stem cells, induced pluripotent stem cells, or adult human RPE stem cells. Utilizing animal models of RPE and retinal degeneration, stem cell-derived RPE cells have been successfully implanted into the subretinal space. They have been injected as a cell mass or as a pre-prepared monolayer on a thin membrane. Visual recovery has been demonstrated in a retinal dystrophic rat model. Preliminary data on 2 human subjects also demonstrates possible early visual benefit from transplantation of stem cell-derived RPE. As more data is published, and as differentiation and implantation techniques are optimized, the stabilization and possible improvement of vision in individuals with non-exudative macular becomes a real possibility. We conclude that the technologic advances that continue to unfold in both genetic and stem cell research offer optimism in the future treatment of AMD.

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Key words: Age-related macular degeneration; Stem cell therapy; Anti-vascular endothelial growth factor; Gene therapy; Complement factor H; High-temperature requirement factor A1; Age-relateed maculopathy susceptibility 2; Pharmacogenomics; Genetics

Core tip: New therapies for age-related macular degeneration (AMD) such as stem cell transplantation and viral vector delivery are currently under intense investigation. Possible new treatments for both non-exudative and exudative AMD are on the horizon. Human embryonic stem cell derived retinal pigment epithelial cells have been transplanted into the subretinal space in human subjects. Viral vectors that encode proteins with a strong affinity for vascular endothelial growth factor are in clinical trials. In light of these exciting advances in both genetic and stem cell therapy, the future of AMD treatment shows substantial promise.

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INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of blindness in the developed world, surpassing cataracts which were the leading cause in 1990[1]. In the United States, current prevalence of advanced AMD defined as geographic atrophy or exudative macular degeneration is estimated to be at 1.75 million. By 2020, it is predicted that 3 million patients will suffer from advanced AMD[2]. At present, there are effective treatments for the exudative form of AMD[3-7], however, when faced with advanced non-exudative AMD visual loss there is little to offer. Research efforts focused on the biological mechanisms of the disease, utilization of stems cells, and genetically based treatments are currently underway to develop novel human therapies.

RISK FACTORS

AMD is a disease that presents with a wide spectrum of severity - from early small drusen with no visual impact to geographic atrophy or choroidal neovascular membrane formation causing severe visual impairment. Multiple non-modifiable and modifiable risk factors have been implicated.

Age

AMD increases significantly in prevalence, incidence, and progression with increasing age. The Beaver Dam eye studies found that by age 75, 7.1% of patients had late AMD compared to 0.1% in those aged 43-54 and 0.6% in age group 55-64[8,9]. Another, more recent study demonstrated that 57.4% of patients over age 85 had signs of AMD[10].

Genetic risk

One study found that 14% of patients with AMD reported a parental history and 21% reported a sibling history of AMD compared to 1% and 2% respectively in control patients. Examined siblings of affected patients showed a 16% prevalence of intermediate disease and a 23% prevalence of advanced disease[11].

Inflammation

Several studies have shown the presence of complement factor byproducts and complement regulatory proteins in drusen and juxtaposed RPE cells. In one study, RPE cells adjacent to drusen exhibited a phenotype consistent with cellular response to complement attack[12]. The role of the complement pathway has been strengthened by the discovery of complement factor gene associations with AMD[13,14].

Oxidative stress

Retinal pigment epithelium (RPE) cells are prone to damage from oxidative stress due to toxin or light exposure[15-17]. The decreased risk of progression with antioxidant supplementation as seen in the AREDS studies yields further evidence of this important mechanism[18,19].

Other risk factors

Some additional non-modifiable risk factors include female sex, hyperopia, and Caucasian race[8,20,21]. Modifiable risk factors include smoking, elevated HDL cholesterol, atherosclerosis, and obesity[10,22].

HUMAN GENOME PROJECT

In April 2003, at an estimated cost of 2.7 billion dollars, the sequencing of the human genome was completed. The project mapped 3 billion base pairs and is estimated to contain approximately 20500 genes. These genes only make-up 1%-2% of the entire sequence. Human to human variation is approximately 0.1% and is more commonly found in non-coding DNA. The past 10 years have led to numerous discoveries including the identification of about 5000 disease producing genes. With technological advances in gene sequencing, today's cost to sequence the human genome has dropped considerably to approximately 1000 dollars (as compared to 2.7 billion 10 years ago). In addition, what used to take years to decades of collaboration among institutions to discover one gene can be completed by one lab within days to weeks[23].

Genome-wide association studies

Genome-wide association studies (GWAS) involve analyzing variations in single nucleotide polymorphisms (SNPs) in patients with a particular disease compared to controls[24]. Coupled with the International HapMap project[25,26] that is responsible for mapping SNP's, GWAS studies today can evaluate a growing number of genetic loci. The overall goal of GWAS is to identify at risk genetic markers for individuals with multifactorial diseases in which a familial component has been identified. Accurate mapping may provide information about disease phenotype, predict genetic markers associated with disease progression, and lead to tailored risk reduction techniques and treatment options. Some limitations of GWAS include: the discovery of many SNPs that are not related to disease, expense, and the requirement of large studies in order to identify a modest risk association[24,27].

AMD GENETICS DISCOVERY

Complement factor H

In 2005, the first GWAS for AMD was published in which a major susceptibility locus was identified. A SNP rs1061170 in the complement factor H (*CFH*) gene in chromosome 1 was shown to have a high association with AMD. SNP rs1061170 encodes a tyrosine to histidine change at the 402 position of the gene (*Y402H*). Complement Factor H inhibits the conversion of C3 to its C3a/C3b components and competes with Factor B to prevent activation of C3b to C3bB[13,14]. A meta-analysis

of eight studies showed that a single allele (heterozygous for risk *Y402H* allele, CT genotype) confers a 2.5-fold increased risk of AMD, while those homozygous for the risk allele (CC) had a 6 fold increased risk. Predicted population attributable risk (PAR) in the same meta-analysis for the risk genotype (CC or CT) was 58.9%[28]. Meta analyses in Asian and Chinese subjects demonstrated a similar increase in risk of AMD per C allele, but a lower PAR[29,30].

OTHER ASSOCIATED GENES

In a meta-analysis in 2005, Fisher *et al*[31] showed a significant link between the locus 10q26 and AMD. Age-related maculopathy susceptibility 2 (*ARMS2*), and high-temperature requirement factor A1 (*HTRA1*) are genes in this locus (10q26) and variations confer a significant risk for AMD that may be higher than with CFH[32,33]. Conversely, polymorphisms of the genes for complement factor B and complement component 2 seem to confer a protective effect to the development of AMD[34-36].

POTENTIAL IMPACT ON MANAGEMENT

Commercial AMD genetic testing has been available for screening at risk patients for several years. However, the value of screening is limited due to the lack of understanding of the association between genetic mutations, modifiable risk factors, and the current therapeutic options. It would be useful to target specific lifestyle modifications in patients depending on their genetic make-up. In addition, if disease progression could be predicted by analyzing the genetic profile of an individual, decisions about the frequency of monitoring and the institution of early intervention could be tailored accordingly[37]. The data however remain conflicting and limited.

GENETIC IMPACT ON CERTAIN RISK FACTORS

Smoking

Several studies show a strong association between smoking and advanced AMD in patients with at risk genes. DeAngelis *et al*[38] showed 144 fold increased risk of CNV in patients who had a 10 pack-year smoking history and were homozygous for the at risk CFH variant compared to individuals who smoked less than 10 pack-years and were heterozygous for the at risk variant, or those who carried the non-risk gene[38]. Similar results were noted for patients with variant at the 10q26 locus[39,40]. Since smoking is an independent risk factor for progression of disease, the effect of smoking in individuals with the risk genotype yields a multiplicative effect[38].

Obesity

AREDS showed a body mass index > 25 did not increase the risk of AMD in patients with a non-risk CFH genotype, however, those who were heterozygous or homozygous for the risk variant showed increased risk with an odds ratio of 2.2 and 5.9 respectively[41].

Genetic impact on risk of progression

The Beaver Dam Eye study patient cohort looked into the association of the CFH and ARMS2 risk alleles and the natural history of AMD. Persons aged 45 years with no evidence of AMD who had low, intermediate, and high AMD genetic risk groups were estimated to develop early AMD at 33.0%, 39.9%, and 46.5% by age 80 years. Late AMD was estimated at rates of 1.4%, 5.2%, and 15.3%, respectively, for these same groups[42]. In addition, a Spanish study showed significant associations of the rate of progression and growth of geographic atrophy with genetic polymorphisms *CFH Y402H*, *CFH-62Ile* and *CFB-32Gln*[43]. Several other studies showed underlying genotype was associated with development of geographic atrophy but had no implication on progression of disease[44,45].

Pharmacogenomics: Targeting/Tailoring treatment

Therapeutic interventions available for the treatment of macular degeneration have been limited to risk modification, anti-oxidants, laser, photodynamic therapy (PDT) and anti-vascular endothelial growth factor (VEGF) agents. With the discovery of the anti-VEGF agents for the treatment of exudative AMD, choices of regimen, dosing, and frequency have been largely dictated by medication cost, physician preference, and large studies that leave a lot to interpretation by the prescribing physician. Tailoring and targeting treatment to individual patients based on calculated susceptibility of the disease to specific intervention(s) is certainly in the future for medicine. Knowing which anti-VEGF medication would be most effective, ideal injection frequency, and the individual risk of complications (such as drug toxicity or RPE tears) prior to initiating treatment would revolutionize our current approach to anti-VEGF treatment and may reduce unnecessary costs[46].

Genetic studies in AMD therapeutic responses have mixed results thus far.

Antioxidants

Klein *et al*[47] studied 876 patients from the AREDS trial who had category 3 and 4 AMD and showed that AREDS vitamin supplementation resulted in a 68% reduction in the rate of progression in the subgroup with the homozygous non-risk genotype compared to a reduction of only 11% in the subgroup with the homozygous risk genotype of *CFH Y402H*. Further analysis revealed the interaction to be explained by zinc. Interaction was noted in the groups taking zinc when compared to those not taking zinc. However, the authors did not feel their results justified routine screening. No genetic treatment interaction was noted for patients with LOC387715/ARMS2[47].

Awh *et al*[48] studied 989 patients from the AREDS trial and showed that patients with a 1 or 2 CFH at risk alleles benefited from antioxidants and not zinc and that

patients with ARMS2 at risk alleles benefited from zinc only regimens[48]. Patients with at risk ARMS2 and CFH alleles showed no benefit to any of the AREDS supplementation. The authors recommended that patients with moderate AMD would benefit from selective nutritional supplementation based on genetic profile[49].

Both studies derived their cohort from the AREDS trial and yet the results are different. However, the AREDS trial was a prospective study that wasn't designed to look into a genetic treatment interaction. Statistically, these studies were too underpowered to achieve statistical significance. In 2012, a task force from the American academy of ophthalmology advised against genetic testing for AMD and that recommendation is unlikely to change with the current evidence[50].

Photodynamic therapy

Initially, 2 small studies have suggested a possible association between CFH and PDT response, but their results were conflicting. In 2008, Goverdhan *et al*[49] published a study of 27 patients and showed that patients carrying 2 CFH at risk alleles responded poorly to PDT compared to other groups. This study was limited by the small sample size. Brantley *et al*[51] looked at a group of 69 patients and showed that in patients with classic CNV, response to PDT was worse for patients with no risk alleles compared to those with one or two at risk alleles[51].

Additional studies with larger sample sizes did not show any association between CFH variants and response to PDT. The largest study of 273 Australian patients looked into this association and found no significant difference in CFH genotypes and response to PDT[52].

Chowers *et al*[53] looked at the association of response to PDT and CFH in an Israeli population of 131 patients and showed no significant association between the genetic variants and response to PDT and number of PDT sessions needed[53]. The same team evaluated the association of PDT response to ARMS2/HTRA1 and showed no significant association between the different genetic variants and the response to PDT or the number of PDT sessions required[54].

Anti-VEGF

Anti-VEGF agents have also been explored. Initially, several studies showed a potential association CFH genotype and response to anti-VEGF response. One group found that intravitreal bevacizumab was associated with worse visual outcomes in patients with the *CFH Y402H* risk genotype[55]. The same group found in a different study that patients with the high risk genotype may require more injections of ranibizumab, but that there was no impact on visual acuity[56]. Hagstrom *et al*[57] recruited 834 patients participating in the Comparison of AMD Treatment Trials (CATT). Each patient was genotyped for rs1061170 (*CFH*), rs10490924 (*ARMS2*), rs11200638 (*HTRA1*), and rs2230199 (*C3*). The study showed no significant difference in patients with high risk alleles (*CFH*, *ARMS2*, *HTRA1*, *C3*) compared to low risk allele in final vision, change in vision, anatomical outcomes (OCT, FA, thickness, lesion size) or number of injections whether bevacizumab or ranibizumab was used[57].

Association between polymorphisms in VEGFA and VEGFR and the response to bevacizumab and ranibizumab were explored. Several studies showed a treatment benefit to anti-VEGF agents, however these studies were limited by the small sample sizes and the limited standardization of their outcomes[58-60]. Hagstrom *et al*[61] showed a different conclusion in a cohort of patients from the Comparison of AMD Treatment Trials. They recruited 835 patients participating in CATT and the patients were genotyped for 7 SNP's in *VEGFA* gene and 1 SNP for *VEGFR2* gene. Results showed no association between the studies genotypes and vision or number of injections[61].

Despite the limited results with AMD, successful examples of genotype directed interventions do exist in other areas of medicine. For example, the drug Abacavir, a reverse transcriptase inhibitor has been associated with an uncommon but potentially fatal and unpredictable hypersensitivity reaction in Human Immunodeficiency Virus patients. In a study published in the New England journal of Medicine, patients with HLA B5701 allele have a 50% chance of developing hypersensitivity while patients without the allele have no risk of developing the hypersensitivity reaction. It is now the standard of care to test patients for this allele prior to starting Abacavir[62].

GENE THERAPY

An emerging therapeutic option is to deliver anti-angiogenic genes using a viral vector. This could allow a sustained delivery of the desired peptide. The challenges here lie in the engineering of a vector that will both target a specific cell (retinal pigment epithelial cell) and allow effective translation of the desired protein.

Pigment epithelial derived factor (PEDF) is a potent anti-angiogenic compound. Campochiaro and colleagues completed a phase I clinical trial in individuals with advanced neovascular AMD using Adenoviral vectors expressing human PEDF (AD-PEDF-11). Twenty eight patients received a single intravitreal injection of low or high dose AD-PEDF-11. Results at 6 and 12 mo showed that the median size of the lesion increased by ½ and 1 disc area respectively in the low dose group compared to no change in the lesion area for the high dose group at 6 and 12 mo. A phase Ⅱ is planned in the future[63].

Another potential VEGF blocker is soluble fms-like tyrosine kinase (sFLT), an endothelium specific receptor tyrosine Kinase. It binds to VEGF with high affinity. A phase I trial of 6 patients who were treated with intravitreal ranibizumab on day 0 and day 30 and received a subretinal injection of a high or low dose sFLT-1 integrated into adeno-associated virus serotype 2 (AAV-sFLT) on day 7. Patients were followed monthly with strict ranibizumab retreatment criteria. By day 380, the high dose group gained 12.5 letters, low dose 8.7 and the control untreated group lost 3.5 letters. Re-treatment with ranibizumab was also less frequent in the treatment group than control. Patients treated with AAV-sFLT showed no

significant adverse events[21]. AAV2-sFLT01 is another sFLT viral vector designed to block VEGF function and is currently in a phase 1 trial[64].

BRIEF HISTORY OF STEM CELL RESEARCH

The terminology of "stem cells" - regenerative precursor cells - was first postulated in 1909 by Alexander Maksimov, a Russian histologist[65]. Since that time there have been many advances in our understanding of stem cells and our ability to isolate them. There are several different approaches to obtaining these progenitor cells; some are derived from adult tissues and others from embryos (embryonic stem cells). Embryonic stem cells are totipotent, meaning they can differentiate into any cell type from any of the three germ layers. In addition, embryonic stem cells have the capacity of unlimited, undifferentiated proliferation *in vitro*. Embryonic stem cells express a high level of telomerase activity, which yields a prolonged replicative life span. Human embryonic stem (hES) cells were first successfully isolated from human blastocysts in 1998[66]. The hES cells were initially grown on a mouse embryonic fibroblast feeder layer[66,67]. Further progress allowed the hES cells to be grown on human feeder layers, and avoid the risk of exposure to animal retroviruses[68]. Now techniques are available to grow hES cells using a serum free, sterile generated protein cocktail that avoids the use of human or animal serum, or human feeder layers[69]. Recent studies also demonstrate that hES cells can be successfully isolated from human blastocysts produced by *in vitro* fertilization rather than from ex-utero embryos[66,70].

Inevitably, ethical and moral issues exist in the use of embryonic stem cells for research purposes. In an effort to avoid such controversy, much work has been done to develop pluripotent adult stem cells that are also capable of differentiating into virtually any tissue in the body. These cells are referred to as induced pluripotent stem (iPS) cells. Such iPS cells have been derived successfully both in mice and in humans[71]. In addition to avoiding the many of the ethical concerns, these adult stem cells can be derived from the patient for whom they would be used, potentially minimizing complications such as rejection of donor tissue.

METHODS OF DIFFERENTIATION INTO RPE CELLS

The RPE has become a primary target for stem cell therapy of AMD. The RPE functions include phagocytosis photoreceptor outer segments, supply of nutrients to the retina, absorption of stray light that passes through the photoreceptors, and formation of the blood retinal barrier[72-74]. Dysfunction of this vital cellular layer in macular degeneration ultimately leads to photoreceptor loss and decreased visual acuity. Differentiation of hESC to RPE was first described in 2004; these cells were compared to fetal RPE cells and were found to express RPE specific markers[75]. RPE cells have been successfully derived using various methods such as co-culture on inactivated mouse embryonic fibroblasts coupled with stromal cell-derived inducing activity, utilizing embryoid body formation, as well as exposing the cells to several signaling pathways[72,75-78]. One group utilized to NIC and Activin A to differentiate hES cells to RPE and successfully transplanted them into the Royal College of Surgeons (RCS) rat and demonstrated rescue of retinal function[71].

In addition to differentiating hES cells into RPE, human induced pluripotent stem cells (iPSCs) have also been described[79-81]. RPE derived from iPSCs (iPS-RPE) expressed cell markers similar to RPE from hESCs. A retinal outer segment phagocytosis assay demonstrated similar efficacy in iPS-RPE and hESC-RPE to fetal retinal pigment epithelium[79]. Another group was able to grow iPS-RPE as a monolayer without an artificial membrane and successfully implant it into the RCS rat with restoration of ERG responses[80].

Adult human RPE stem cells (hRPESC) are another source of RPE cells. These cells are derived from elderly donor eyes and expanded to differentiate into RPE cells. One study found that a single donor may be able to provide enough cells to cover hundreds of patients using stem cell proliferation techniques[82]. Further study is needed to determine if these cells are suited for intraocular transplantation.

One study evaluated the essential role of RPE in the proper structural formation of photoreceptors, including the outer segments. Therefore, the ability to create polarized RPE cells may aid in the differentiation of functional photoreceptors for possible therapeutic use in ocular diseases causing photoreceptor dysfunction or death[83]. Overall, a key to developing successful stem cell therapies for AMD is establishing a high-yield, accurate, and reproducible method of differentiating stem cells to RPE that can survive *in vivo*, integrate properly into the host retina, and perform the essential RPE functions.

In addition to the above advances in RPE derivation from stem cells, hESC derived photoreceptors can be successfully implanted into $Crx^{-/-}$ mice with improved ERG responses compared to controls[84]. This may allow for not only photoreceptor rescue but potentially replacement of dead/degenerated photoreceptors in the future.

METHODS OF INTRAOCULAR IMPLANTATION

After isolation of retinal pigment epithelial cells from either hRPESC, iPSC or hESC, the next challenge becomes creating an effective method of intraocular implantation to maximize the therapeutic effect. Two primary techniques have been employed: injection of a cell mass into the subretinal space, or implantation of a monolayer prepared on a thin membrane.

Cell suspension injection techniques

In nude rats a 1.2 mm scleral incision was made 1.5 mm posterior to the limbus and then a local retinal detachment was created by injecting 5 microliters of balanced saline solution. Next, *via* a 32 G blunt-end injection cannula, 2 microliters of phosphate-buffered saline solution containing the hESC-RPE was injected into the subretinal space *via* the sclerotomy site[85]. A different group also utilized a trans-scleral technique in rats, however, no subretinal bleb was created prior to cell suspension injection[86,87].

Thin membrane implantation techniques

Given that the RPE is a single layer of polarized cells it is presumed that the best functional outcome of transplantation would yield a monolayer of new RPE. Injecting a cell mass can lead to clumping of RPE cells rather than the formation of a monolayer. In search for a solution, groups have cultured RPE cells on thin membranes as a monolayer followed by implantation of the membrane-RPE complex into the subretinal space[82,85,88-90].

One group, utilizing chinchilla rabbits, performed a two-port core vitrectomy, then created a small bleb retinal detachment with 25-30 mL of balanced saline solution using a 41 G Teflon cannula. Conventional infusion caused the bleb to flatten during the procedure, therefore a custum-made infusion with 2 side ports was utilized to minimize disturbance of the bleb[88]. The retinotomy was enlarged with scissors and then a polyester membrane lined with hESC-RPE was inserted using a custom-made subretinal shooter instrument[82,88]. Electrostatic adhesions between the implant and the delivery device often required additional maneuvering (with subsequent retinal damage) to successfully place the thin membrane into the subretinal space. Utilizing a hydrogel encapsulation of the implant significantly decreased these hydrostatic forces and improved the success of subretinal placement[88]. Other customized injection instruments have been designed, including one that gently delivers a parylene membrane lined with a monolayer of hESC-RPE using an infusion of balanced salt solution through small holes in the device[90]. A previous group had used a similar technique using an injection instrument and mircoforceps. This group also utilized perfluorocarbon to create an intraocular tamponade to prevent reflux of fluid through the retinotomy site[89].

Another group, utilizing nude rats, compared the injected RPE cells cultured on a parylene membrane into the subretinal space *via* a trans-scleral incision. First, a 1.2 mm scleral incision was made 1.5 mm posterior to the limbus and then a local retinal detachment was created by injecting 5 microliters of balanced saline solution. Next, the choroid was cut, taking care to avoid retinal damage, and the hESC-RPE membrane substrate was inserted into the subretinal space utilizing forceps[85].

In addition to hESC-RPE, hRPESC have also been used and proliferated on a polyester membrane and implanted into rabbit eyes and survive with maintenance of cellular polarity up to 4 wk after graft implantation[82].

IMPACT ON VISUAL ACUITY

Comparison of injection hESC *via* a cell suspension vs hESC cultured on a parylene membrane demonstrated increased cell survival in the polarized monolayer group. In this same study, the rats were observed for up to 12 mo with persistent cell survival and there was no evidence of teratoma or ectopic tissue formation[85]. Another group injected the RCS dystrophic rats with different doses of a subretinal hESC mass (either with 50000 or 100000 hESCs) and found that treated rats demonstrated better spacial acuity when compared to sham and untreated rats. Once again, this study demonstrated no evidence of teratoma or tumor formation (up to 220 d)[87]. Also, utilizing the RCS rats and the cell suspension technique, Lund *et al*[91] demonstrated improvement in vision in the RCS rats that achieved spacial acuity up to 70% of the non-dystrophic rats[91]. Transplantation of iPSCs have also been performed in RCS rats and demonstrated slowed visual decline, however, the transplanted cells were lost to immune response despite immunosuppressive therapy[92].

Human trials

The preliminary results of 2 human subjects, one with Stargardt's macular dystrophy and one with dry AMD are now available. The patients were given low dose tacrolimus and mycophenolate mofetil 1 wk prior to the procedure. HESC MA09 cells were used for implantation. The procedure entailed a pars plana vitrectomy with induction of a PVD from the optic disc followed by the injection of approximately 50000 hESC-RPE (150 microliters) into the subretinal space at a predetermined location based on OCT findings consistent with an area of RPE and photoreceptor compromise. The induced bleb had flattened by 4 h after the surgery in both patients. The patient with Stargardt's disease improved from hand motion to 20/800, and the patient with AMD improved from 20/500 to 20/320. However, it is unclear whether the mild improvement was due to the transplanted cells, immunosuppressive medications, or to placebo effect. In the future as more data are collected we will have a better understanding of the effect of implanted hESC-RPE in the human subretinal space[93].

CONCLUSION

AMD affects millions of people worldwide and is the leading cause of blindness in the United States[1]. As our understanding of molecular medicine has expanded so has our approach to disease treatment. The severe vision loss that almost always accompanied exudative macular degeneration in years past is now being widely treated with anti-VEGF injections[4-7]. Current therapies, including viral vector delivery of VEGF binding proteins, may allow for prolonged VEGF blockage allowing for a significantly reduced number of intravitreal injections[63]. Also, understanding the complex array of genes associated with AMD may allow us to make tailored therapeutic decisions and/or lifestyle recommendations depending

on a patient's genetic make-up[47,52,57,62].

Currently there is no treatment to offer patients with advanced non-exudative AMD, however, stem cell therapy may provide a future solution. Techniques to differentiate hESC (or iPSC and hRPESC) into RPE cells allow for a potentially numberless supply of cells to utilize in transplants to treat not only macular degeneration but also other disorders such as Stargardt's macular dystrophy, retinitis pigmentosa, cone-rod/rod-cone dystrophies, *etc*. More data is required to determine if a single origin of RPE is more effective than the others in creating fully functioning RPE cells. Once the RPE cells are successfully derived, there must be safe, reproducible, and effective method(s) to surgically implant the new cells. There are currently different techniques and instruments under investigation, whether it be by subretinal injection of a cell mass or implantation of a pre-RPE cultured thin membrane, and further study is necessary to determine which technique will yield the best visual outcomes with the least degree of surgical complications. In addition to RPE, studies have also been performed demonstrating that hESC derived photoreceptors can be successfully implanted into mice[85]. This may allow for not only photoreceptor rescue but also potential replacement of dead photoreceptors in the future. In light of these exciting advances in both genetic and stem cell therapy, the future of AMD treatment shows substantial promise.

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Improving refractive outcomes in cataract surgery: A global perspective

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Abstract

This review summarises the current evidence base and provides guidelines for obtaining good refractive outcomes following cataract surgery. Important background information is also provided. In summary, the requirements are: (1) standardisation of biometry equipment used for axial length and keratometry measurement and the use of optical or immersion ultrasound biometry; (2) sutureless cataract surgery with "in the bag" intraocular lens (IOL) placement; (3) an appropriate 3rd, 4th or 5th Generation IOL power formula should be used; (4) IOL formula constants must be optimized; (5) under certain conditions, the refractive outcome of the 2nd eye can be improved based on the refractive error of the first eye; and (6) results should be audited for refinement and to ensure that standards are met.

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Key words: Biometry; Cataract extraction; Ocular refraction; Intraocular lens; Intraocular lens Power Formula

Core tip: The requirements for good refractive outcomes in cataract surgery are: (1) standardisation of biometry equipment used for axial length and keratometry measurement and the use of optical or immersion ultrasound biometry; (2) sutureless cataract surgery with "in the bag" intraocular lens placement; (3) an appropriate 3rd, 4th or 5th Generation intraocular lens (IOL) power formula should be used; (4) IOL formula constants must be optimized; (5) under certain conditions, the refractive outcome of the 2nd eye can be improved based on the prediction error of the cataract surgery for the first eye; and (6) results should be audited for refinement and to ensure that standards are met.

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INTRODUCTION

Advances in technology and improvements in technique have made cataract surgery safe and effective at restoring vision to millions of patients worldwide. Phacoemulsification with intracapsular intraocular lens (IOL) implantation has been universally adopted in developed countries and manual small incision cataract surgery has revolutionized service delivery elsewhere. Achieving the desired refractive outcome is now a primary aim of surgery and so can be used as a measure of the quality of clinical services. In developed countries, patients expect reduced spectacle dependence and in developing countries residual uncorrected high refractive error remains an important cause of visual disability, which can be caused by

inappropriate selection of IOL power at surgery[1]. This article reviews the evidence base and offer guidelines to achieve optimal refractive outcomes.

THE INFLUENCE OF SURGICAL TECHNIQUE ON REFRACTIVE OUTCOMES

Conventional extracapsular cataract surgery with a large corneal section requiring sutures has declined in popularity. Its main disadvantages were the delay in visual rehabilitation due to the induction of corneal astigmatism as well as the need to remove corneal sutures following surgery[2]. Furthermore, sulcus IOL placement, makes the actual post-operative IOL position, and hence refraction, less predictable[3]. Continuous curvilinear capsulorhexis allows for predictable placement of the IOL in the capsular bag and small self sealing corneal incisions induce less post-operative astigmatism[4-6]. Manual small incision cataract surgery can also result in low amount of induced astigmatism, especially when a temporal approach is used[7].

Optimal refractive outcomes can be achieved both in phacoemulsification and small incision manual cataract extraction when the following conditions are met: (1) reproducible measurement of axial length and keratometry (preferably but not necessarily with optical biometry), (2) good surgical technique with a low rate of posterior capsular rupture; (3) in-the-bag IOL placement and a capsulorhexis size smaller than the optic diameter; (4) appropriate choice of IOL power formula and, most importantly, (5) availability of post operative refraction; and (6) adjustment of the IOL formula constant (optimization) for the specific IOL model and the specific methods of biometry used.

BIOMETRY METHODS

The measurement of the physical dimensions of the eye is necessary to calculate the intraocular lens power. The minimum measurements required are axial length and corneal power. Many suitable devices can take these measurements but all these have systematic differences in measurement. It is therefore very important that the intraocular lens formula is used with the correct formula constant that corrects for these systematic differences in measurement[4]. This not only applies for the axial length measurement method but also for the keratometry method.

Axial length measurement

Axial Length measurement can be performed using ultrasound or optical methods. Optical methods use partial coherence interferometry or low coherence reflectometry[8]. Their advantages over ultrasound methods are that they are non-contact, precise and reproducible and have a low dependence on operator skill. Optical methods are considered to be the standard of care in developed countries. Nevertheless, they are more expensive and less portable than ultrasound methods and cannot provide measurements in the presence of dense axial lens opacities. Contact ultrasound methods give systematic errors in measurement of the axial length due to the inadvertent compression of the cornea[9] and the magnitude of error is influenced by the operator experience[10]. Immersion ultrasound techniques do not cause corneal compression and can deliver refractive outcomes similar to optical methods[11].

Keratometry

Modern optical biometry devices have in-built keratometers, which enable very good refractive outcomes with respect to correcting spherical error. It is outside the scope of this review to discuss the assessment and correction of astigmatism at the same time as performing cataract surgery. Published optical IOL formula constants for each IOL model are derived from axial length and keratometric data obtained from each device. These published IOL constants can be used with confidence by surgeons when they start using a new IOL model, provided they are using the same instrument.

Combining separate axial length and keratometry instruments (when for example ultrasound is used for axial length measurement) can also give very good results but departments must make sure that they optimize their IOL formula constants based on their data for the specific set of instruments used. Manufacturers' IOL constants can not be relied upon for good refractive outcomes.

Other biometric measurements

Newer biometry formulae use one or more of the following biometric measurements: Anterior Chamber Depth, Lens thickness, White to White diameter, age and preoperative refraction. The benefits of using these additional measurements are not proven and excellent results can be obtained using a combination of 3rd generation IOL formulae with optimized IOL constants.

Choice of biometry instruments

For established eye departments where the supply of electricity is reliable, optical biometry has clear advantages over ultrasound biometry as very precise measurements can be obtained quickly and without any contact of any instrument with the eye. In the setting of limited resources, ultrasound axial length measurements can offer good outcomes, especially when an immersion technique is used. The added time required for traditional immersion techniques with a shell have been a limiting factor with respect to their adoption as it would affect the flow of patients in high volume practices. Newer immersion techniques include the use of a clip-on attachment that requires minimal amount of saline or the use of lubricant eye gel as a coupling agent. These immersion techniques are more time efficient than using a traditional immersion shell and offer advantages in precision over contact methods. In cases where electricity supply is not reliable, both ultrasound biometry and keratometry are available as portable battery operated units. Some portable

Table 1 Available intraocular lens power formulae

Name of formula	Variables required	Comments
SRK I and Binkhorst I 1st Generation	Keratometry, Axial Length	Obsolete High levels of error, should not be used
SRK II and Binkhorst II 2nd Generation	Keratometry, Axial Length	Obsolete High levels of error, should not be used
Holladay 1 3rd Generation	Keratometry, Axial Length	Trend toward better outcomes for eyes between 22.00 mm and 26.00 mm, compared to other 3rd generation[14]
SRK/T 3rd Generation	Keratometry, Axial Length	Better outcomes for eyes over 26.00 mm, compared to other 3rd generation formulae[14]
Hoffer Q 3rd Generation	Keratometry, Axial Length	Better outcomes for eyes under 22.00 mm, compared to other 3rd generation[14]
T2 3rd Generation	Keratometry, Axial Length	Very good outcomes for eyes over 22.00 mm[15] It corrects the cusp phenomenon, an error observed using the SRK/T on certain eyes[16]
Holladay 2 4th Generation	Keratometry, Axial Length, Anterior Chamber Depth, Lens Thickness, Horizontal White to White, Age, Pre operative refraction	No data has been reported showing an advantage over an appropriately selected 3rd generation formula
Olsen 4th Generation	Keratometry, Axial Length, Anterior Chamber Depth, Lens Thickness, Horizontal White to White	There is eidence suggestive of improved performance over 3rd generation formulae for eyes with axial length between 20.00 and 26.00 mm[17,18]
Haigis 5th Generation	Keratometry, Axial Length, Anterior Chamber Depth	Very good outcomes for eyes across the axial length range and best reported outcomes for eyes longer than 28.00 mm[19] For best results, three IOL constants need to be optimized requiring data from at least 500 eyes

IOL: Intraocular lens.

keratometers are combined with an autorefractor, which is very valuable as IOL constant optimization depends on the availability of post-operative refraction data. The international agency for the prevention of blindness publishes a standard list of equipment for Vision 2020 eye care service units and this can be used for guidance[12,13].

IOL POWER FORMULAE

The evolution of IOL power calculation formulae has consistently improved the predictability of refractive outcomes, since Fyotorov's first IOL formula. There are now a plethora of IOL formulae but only some of these are still considered fit for purpose. Table 1 summarizes the IOL formulae found in biometry instruments, along with comments for each one.

Outcomes with single power implantation

Implanting a single power IOL without biometry assessment used to be common in developing countries as it was said that certain populations do not have as high variability in axial length as in developed countries[20]. Nevertheless, choosing an appropriate IOL power based on pre-operative biometry promises improved unaided vision[21] and much more predictable refractive outcomes. Many patients in developing countries do not have access to optical correction and therefore high refractive errors are a significant cause of visual disability[22].

Outcomes with formulae using two biometric variables (Axial length and Keratometry)

For the majority of cataract surgery cases worldwide, the biometric measurements that can be practically assessed are axial length and keratometry. These can be performed at a low cost using portable battery operated instruments. Using axial length and keratometry, the refractive outcomes of cataract surgery have the potential to reach a very high level of accuracy and precision provided that a number of conditions are met.

An appropriate 3rd generation IOL power formula should be used: The Hoffer Q should be used for eyes less than 22.00mm, the Holladay 1 should be used for eyes between 22.00 and 26.00 and the SRK/T is more appropriate for eyes over 26.00 mm. These formulae are available in commercial biometry instruments. The T2 formula has addressed a source of error inherent to the SRK/T formula, called the cusp phenomenon and can therefore be used in eyes 22.00 or longer[15]. Although the T2 formula has been published, it is not currently included in commercial biometry products. The formula is available as an Excel spreadsheet at http://www.richardsheard.net/T2Formula.aspx. Previous generation two-variable formulae are obsolete and should not be used. These include the SRK- Ⅰ, SRK Ⅱ, Binkhost Ⅰ and Ⅱ, and the original Hoffer formula.

An optimized IOL constant should be used: The IOL constant value depends on (1) the IOL model; (2) the biometry instruments used; and (3) the position of the IOL implantation (in the bag *vs* sulcus). These factors are far more important than any differences between surgeons, something formerly thought to be important. Indeed for small incision phacoemulsification surgery and optical biometry it has been demonstrated that there are no significant differences between most surgeon's optimized constants, only between methods of measurement.

It is worth noting that using manufacturer's (non-

optimized) constants even with an appropriate 3rd generation IOL formula can give very poor refractive outcomes, which are usually in the hyperopic direction when using optical biometry[4]. The IOL constant that is contained on the IOL packaging is often not appropriate for IOL calculations. When starting to use a new IOL implant, it is suggested that published IOL constants are used[23]. For ultrasound biometry, the manufacturer may have data to help departments until they have enough cases to optimize their own IOL constants.

If an incorrect IOL constant is used, the formula would give results which are systematically skewed towards the hypermetropic or myopic end and result in consistently poor outcomes. The optimization of the IOL constant "resets" the mean error of the formula to 0. This means that on average the refractive aim and the post op refraction are the same. From there on, the method of biometry and the appropriateness of the IOL formula help minimise the distribution of errors.

IOL power formulae using three or more biometric variables

The Holladay 2 was the first published formula that used these variables, but its code has never been available in the public domain. Later on, Thomas Olsen and Wolfgang Haigis separately published their own eponymous IOL formulae and these have been published[17,24]. The evidence so far suggests that the Olsen formula has a statistically significant advantage over the Hoffer Q, the Holladay 1 and the SRK/T in eyes between 20.00 and 26.00 mm[17,18]. The Haigis formula with all three IOL constants optimized has been found to perform very well across the axial length range as well as giving a lower prediction error in very myopic eyes, compared to the SRK/T[19]. We could not find any published evidence showing that the Holladay 2 formula performs better than an appropriately selected 3rd generation IOL formula.

ACHIEVING HIGH ACCURACY AND PRECISION IN REFRACTIVE OUTCOMES

The need to describe and quantify refractive outcomes arises from the fact that in many cases, the predicted postoperative refraction is not the same as the actual (or observed) post operative refraction. Observed refraction minus the Predicted Refraction is the Refraction Error. For example if for a patient the refractive aim with the chosen IOL power is -0.53 D and the actual post operative result was -0.25 D, then the Prediction Error for this eye would be +0.28D.

When describing refractive outcomes for a large sample of eyes, the measures need to quantify: (1) how close to zero the average prediction error of this sample of eyes is (Mean Error); and (2) how widely dispersed are the errors spread around this mean. The approach of choosing an appropriate IOL power could be likened to a rifle competition. The success of using a rifle depends not only on the technology of the aiming device it carries but also on whether the aiming device has been appropriately calibrated. Mean Error is a measure of Accuracy, *i.e.*, an AVERAGE measure of how close most shots hit the target. On the other hand, Precision represents the spread of the shots around the mean, and this can be measured by the Standard Deviation of the Prediction Error. Figure 1 gives examples of targets shot with: (1) High Accuracy and High Precision; (2) High Accuracy and Low Precision; (3) Low Accuracy and High Precision; and (4) Low Accuracy and Low Precision.

In the same way, in order to achieve good refractive outcomes in cataract surgery, it is not enough to use appropriate biometry methods and formulae. The calculations need to be calibrated (or optimized) in order to achieve the target refraction for the majority of eyes. The availability of good biometry methods and modern biometry formulae has improved the precision of achieving the refractive target. Nevertheless, this is not enough and surgeons need to use an appropriately Optimized Formula Constant for the particular IOL model used in order to correct the accuracy of the results. There is a very good example of an eye department in the United Kingdom, which made the transition from ultrasound to optical biometry and subsequently audited their refractive outcomes[25]. Their initial results showed that when the manufacturer's IOL constant was used with optical biometry, patients became on average 0.63D more hypermetropic than expected with only 65% achieving refraction within 1.0 Dioptre from target. Following adjustment of the IOL constant based on audit results, the Mean Error was reduced to -0.14D and 95% of cases achieved refraction within 1.0D of their target. Using the rifle paradigm, the move from ultrasound to optical biometry can be likened to an upgrade of the aiming device of the rifle. The new aiming device was not calibrated and therefore was consistently resulting in shots hitting +0.63D away from target, despite the fact that these shots were tightly grouped. The adjustment of the IOL constant moved the average deviation closer to zero.

Optimizing the IOL constants provides a greater magnitude of improvement in results than choosing the correct IOL formula for a given axial length range[14].

GUIDELINES FOR OPTIMIZING THE IOL CONSTANT

When using a new IOL model, formula constants should be obtained from a reputable source such as the manufacturer or the ULIB website and should be appropriate for the method of measurement used (*i.e.*, for the specific instruments used for axial length and keratometry measurement). The refractive outcomes using this IOL model should be audited and once more than 100 eyes are obtained, the IOL constant may be modified in order to improve future refractive outcomes.

Most IOL constant optimization protocols define a minimum post operative time period from cataract surgery for refractive data collection. This is usually set at 1

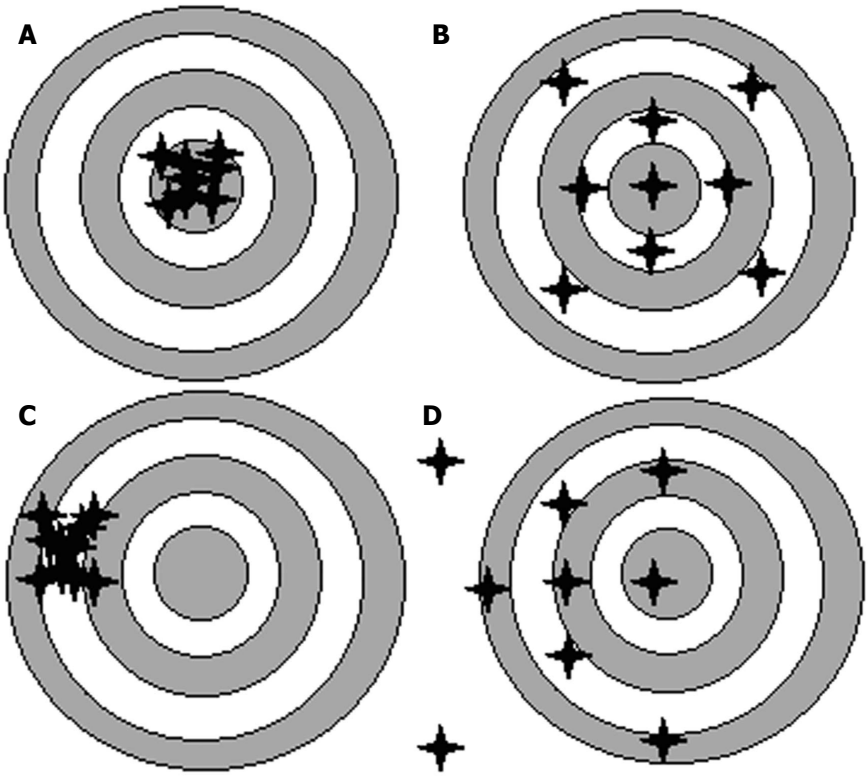

Figure 1 Examples of changing accuracy and precision on a shooting target. A: High accuracy and high precision; B: High accuracy and low precision; C: Low accuracy and high precision; D: Low accuracy and low precision.

month, by which time post operative refraction is considered stable. This should be the standard for most eye units. In situations where patients travel a large distance and they are only available on day 1 post operatively (such as in eye camps), day one autorefraction is a reasonably reliable source of post op refraction, which can be performed by non medical staff and therefore have a small impact on staff resources[21]. In such circumstances cases, day one best corrected visual acuity of 6/18 may be used as the minimum level of VA in order for cases to be included for IOL constant optimization.

DATA REQUIREMENT AND SELECTION OF EYES

For 3rd generation IOL formulae, there should be around 100 such eyes to calculate an optimized IOL constant. The data required are: (1) preoperative Axial length; (2) preoperative keratometry; (3) IOL model and power used; (4) IOL constant used; (5) post operative refraction (spherical equivalent); and (6) post operative visual acuity. Appropriate eyes for inclusion are those that had uncomplicated cataract surgery with in the bag IOL implantation and a final best corrected visual acuity of 6/12 or better (or minimum BCVA 6/18 for day 1 refraction in eye camps). Eyes that had coexistent corneal pathology such as pterygium and keratoconus or concurrent surgery such as trabeculectomy, corneal surgery or vitrectomy should be excluded. It is worth noting that the same sample of eyes containing the full range axial lengths can be used for optimizing the Hoffer Q, the Holladay 1 and the SRK/T even though the Hoffer Q formula is recommended for eyes shorter than 22 mm. If optimization relied only on eyes < 22 mm in length a very large number of cataract operations would be required to include 100 eyes under 22 mm in length.

METHODS OF OPTIMIZING IOL CONSTANTS FOR 3RD GENERATION IOL FORMULAE

With some electronic patient records or with optical biometers such as the Zeiss IOLMaster or the Haag-Streit Lenstar 900, there are inbuilt processes in its software for automatically calculating optimized IOL constants. When these are not available, data can be processed manually. One option is to use a validated iterative method where the IOL constant for each eye is retrospectively calculated so that the post operative prediction error is 0. These IOL constants are then averaged (after excluding 5% outliers on each side of the distribution). This method requires access to specialized software as well as having a high level of programming skills. A third option would be to manually estimate a close approximation of the optimized IOL constant, which does not require specialized IT skills or equipment. Using (1), (2), (3) and (4) from the list above, the predicted refractive error is calculated for each eye. Subtracting the post operative refraction from the predicted refraction in each eye gives the prediction error for each eye. When the average prediction error

is calculated for a sample of 100 suitable eyes, the IOL constant is increased if the average prediction error is hyperopic or reduced if it is myopic. The magnitude of IOL constant alteration can be calculated in the following manner: For each 0.1 Dioptre of hyperopic error, the following adjustments need to be made: 0.06 for the pACD(Hoffer Q), 0.06 for the SF (Holladay 1) and 0.12 for the AC (SRK/T)[4]. For example, if for a specific IOL model the average prediction error for 100 appropriate eyes was +0.53D using a pACD of 4.97, an SF of 1.22 and an AC of 118.0, the following optimization would need to be made. For the pACD the new constant would be increased by 0.318 to 5.288, for the SF the constant would be increased by 0.318 to 1.538 and for the AC it would be increased by 0.636 to 118.636. In practice, the IOL constants for 3rd generation formulae are used to an accuracy of 2 decimal places for the pACD and the SF and one decimal place for the AC.

FURTHER OPTIMIZATION OF REFRACTIVE OUTCOMES: IMPROVEMENTS FOR THE 2ND EYE

If the IOL constants are optimized and appropriate IOL formulae are used, refractive outcomes can be further improved when operating on the 2nd eye of a patient. It has been calculated[26-28] and prospectively validated[29] that the second eye can obtain improved refractive outcomes by modifying its refractive aim by half of the prediction error of the first eye. For example, if the first eye of a patient had a prediction error of +0.64D following surgery, the second eye should be aimed at -0.32D from the intended refraction. The requirements for this method to be applicable are: (1) in the bag IOL placement for both eyes; (2) the same IOL model and formula used in both eyes ;(3) interocular difference in keratometry of less than 0.6D; and (4) prediction error for the first eye +/-1.5D or less[27]. The same IOL formula should be used in both eyes and an optimized IOL constant should be used. This relationship has been demonstrated with the Hoffer Q, the Holladay 1, the SRK/T and the Olsen formulae. All papers were based on data obtained using optical biometry so this should not be used for eyes measured with contact ultrasound. No recommendation can be made for immersion ultrasound.

ADDITIONAL CONSIDERATIONS FOR REFRACTIVE PLANNING IN CATARACT SURGERY

This article is aimed at a worldwide audience and aims to review the evidence on predicting spherical prediction error following cataract surgery, which globally is the most important refractive determinant of visual function following cataract surgery. In any surgical setting, may this be a tertiary centre in an economically fully developed country or an eye camp in a developing country, minimizing spherical refractive error should be one of the primary aims of cataract surgery. The relative importance of other factors that may be considered greatly depend on the resources available. These include the management of corneal astigmatism[30], concurrent correction for presbyopia using a variety of intraocular lens designs[31] and the use of femtosecond lasers[32]. It is not in the scope of this review to assess the evidence on the management in these situations.

STANDARDS FOR REFRACTIVE OUTCOMES

Using an appropriate 3rd generation IOL formula with optimized constants and optical biometry with phacoemulsification and intracapsular IOL placement, around 70% and 95% of eyes can achieve refraction within ± 0.50D and ± 1.00D of the refractive target, respectively[14]. Using immersion ultrasound, similar results to optical biometry can be obtained as long as optimized IOL constants and appropriate 3rd generation IOL power formulae are used[33].

CONCLUSION

Refractive outcomes are a very important aspect of cataract surgery in any clinical setting. Good results primarily depend on the use of optimized IOL constants and appropriate IOL formulae. Clinical audit of post operative refraction is required in order to validate and refine IOL constants. The availability of optical biometry has enabled further improvements by the efficient capture of precise data but in departments where optical biometry is not available, very good outcomes can be obtained using modifications of immersion ultrasound technique and optimizing the IOL constants for the particular department.

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MINIREVIEWS

Current evidence of pathophysiology of diabetic macular edema: A review

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Abstract

Diabetic macular edema (DME) is an important cause of vision loss in patients with diabetes mellitus. The pathophysiology of DME can be described as a process whereby hyperglycaemia leads to overlapping and inter-related pathways that play a role not only in the initial vascular events, but also in the events that cause the edema to become chronic. On a macrocellular level, DME is believed to be in part caused by alterations in hydrostatic and oncotic pressures and shear stress. Angiogenic factor expression, inflammation and oxidative stress constitute the key components of microvascular pathways. The interactions, signalling events and feedback loops between the various molecules are complicated and are not completely understood. These molecular mediators, acting in conjunction with macrocellular factors, which are all stimulated in part by the hyperglycaemia and hypoxia, can have a direct endothelial effect leading to hyperpermeability, disruption of vascular endothelial cell junctions, and leukostasis. Macular edema is thought to be caused as a result of these consequences.

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Key words: Diabetes mellitus; Macular edema; Pathophysiology; Vascular endothelial growth factor; Inflammation

Core tip: Diabetic macular edema (DME) is an important cause of vision loss in patients with diabetes mellitus. The pathophysiology of DME can be described as a process whereby hyperglycaemia leads to overlapping and inter-related pathways that play a role not only in the initial vascular events, but also in the events that cause the edema to become chronic. On a macrocellular level, DME is believed to be in part caused by alterations in hydrostatic and oncotic pressures and shear stress. Angiogenic factor expression, inflammation and oxidative stress constitute the key components of microvascular pathways. The interactions, signalling events and feedback loops between the various molecules are complicated and are not completely understood. These molecular mediators, acting in conjunction with macrocellular factors, which are all stimulated in part by the hyperglycaemia and hypoxia, can have a direct endothelial effect leading to hyperpermeability, disruption of vascular endothelial cell junctions, and leukostasis. Macular edema is thought to be caused as a result of these consequences.

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INTRODUCTION

Most common reason of visual loss in diabetes mellitus (DM) is diabetic macular edema (DME)[1,2]. Macular edema can develop in any stage of the disease but the risk increases as the disease progresses[3]. The role of hyper-

glycemia on development of DME has been investigated in a population based study, Wisconsin Epidemiologic Study of Diabetic Retinopathy (DR). In this study, the risk of developing DME in 10 years is reported as 20.1% in type I DM, 13.9% in noninsulin-dependent type Ⅱ DM and 25.4% in insulin-dependent DM patients[4].

The classification of DME has changed over time as new imaging techniques have evolved. DME is classified as clinically significant according to visible retinal thickening and hard exudates in relation to distance from macula in Early Treatment Diabetic Retinopathy Study. In Global Diabetic Retinopathy Project, mild, intermediate or severe DME have been described according to the severity of involvement of macular center in light of ocular coherence tomographic findings[5,6].

Since the macular edema in presence the of DM may lead to permanent visual loss, it is of great importance to understand the pathophysiology of DME in order to prevent this complication and to develop new treatment strategies. The factors leading to development and progression of DME and the macrovascular and microvascular changes induced by DM are summarised in this review.

GENERAL INFORMATION

Why is the macula involved?

Even though there is a generalized micro vascular damage and vascular leakage throughout the retina, there are some predisposing histological and metabolic properties of the macula that render it prone to edema: (1) high cellular concentration; (2) high metabolic activity; (3) the oblique-horizontal course of Henle fibers toward periphery; (4) weak intercellular junctions in the external plexiform layer; and (5) presence of central avascular zone.

Normal retinal circulation and blood-retinal barrier

Among the tissues in the body, retina is one of the tissues with highest oxygen requirement and is supplied by two different circulations. Inner 2/3 of retina is supplied by retinal circulation and outer 1/3 is supplied by choroidal vessels. Endothelial cells on vascular wall and the surrounding pericytes and astrocytes constitute the inner blood retinal barrier. Outer blood retinal barrier is formed by tight junctions between the cells of retinal pigment epithelial (RPE) layer.

In retinal circulation, arteries branch into precapillary arterioles which are surrounded by smooth muscle cells controlled by autonomic nervous system. Beyond this level, in the capillary layer, pericytes take place of smooth muscle cells and the flow rate is determined by autoregulation. Under normal circumstances, capillaries and venules are primary sites of fluid passage and the flow changes according to local metabolic needs, oxygen and carbon dioxide partial pressures. In the early stages of diabetic retinopathy, there is damage to inner blood retinal barrier and the increased filtration of fluid from capillaries and venules result in macular edema.

PATHOPHYSIOLOGY

There are numerous pathophysiologic mechanisms that have been proposed as the role of diabetes on development of DME. But, the exact mechanism of the damage to the blood-retinal barrier caused by hyperglycemia is not known. Several pathways involving angiogenic and inflamatory factors and oxidative stress are considered to take role.

Macrovascular effects of diabetes

In all tissues including retina, the movement of fluid and particles across vascular wall depend on intravascular and extravascular hydrostatic and oncotic pressures. According to Starling's Law, equilibrium is reached when the differences between intra and extravascular the oncotic and hydrostatic pressures are equal. In retina, capillary hydrostatic pressure is related with systemic blood pressure, and the oncotic pressure is related with the albumin level that constitute majority of serum proteins. Tissue hydrostatic pressure is equal to intraocular pressure and tissue oncotic pressure is related with interstitial protein content. This equilibrium is disrupted in case of diabetes by several factors. Increased transluminal hydrostatic pressure due to hypertension and increased tissue oncotic pressure due to blood- retinal barrier damage and leakage of intravascular proteins into the interstitial space result in retinal edema. If a there is coexistent diabetic nephropathy, the decreased serum albumin levels lower intravascular oncotic pressure which contribute to edema[7].

There are animal models which show increased ocular blood flow in case of increase in blood glucose levels. It is also reported that acute increases in plasma glucose levels cause increase in ocular blood flow in human studies. Increased thromboctye aggregation, decreased erythrocyte deformability and increased blood flow cause an increase in shear stress on the vascular endothelial cells. The resulting secretion of vasoactive and inflammatory factors contribute to the pathological process on the molecular level[8,9].

Microvascular effects of diabetes

Pericyte loss is the earliest and most specific sign of diabetic retinopathy. Cogan *et al*[10] have shown the loss of the pericytes as ghost cells surrounding the capillary walls. The mechanism of pericyte loss in diabetes is not clearly known. Pericytes express advanced glycosylation endproducts (AGE) receptors and thus may be susceptible to damaging effects of AGEs. Additionally, it may be indirectly related to the leukocyte adhesion to the vasculature[11].

Pericyte loss is the first sign that can be shown histologically, whereas the first clinical sign of diabetic retinopathy that can be shown by fundus examination and fundus flourescein angiography is microaneurysm formation. Pericytes exert antiproliferative effect on endothelial cells and their loss results in hypercellular microaneurysm formation. Hypocellular aneurysms are thought to be formed by apoptosis of these proliferated endothelial

cells. Pericyte loss also results in loss of support around the vascular wall which leads to focal dilatations at the weak points contributing to microaneurysm formation[10].

Thickening of the capillary basal membrane and accumulation of the extracellular matrix elements are shown in diabetes retinopathy. It is thought that these changes result in abnormal autoregulation of vascular flow and retinal hemodynamic instability.

Endothelial cells have intercellular tight junctions which act as barrier to intravascular components. These junctions are formed by numerous intercellular proteins including occludin, claudin and zonula occludens-1 which are responsible for most of the barrier function. In diabetes, the synthesis and expression of these proteins are affected resulting in weakening of intercellular bonds.

Combined effect of loss of pericytes, microaneurysm formation, basement membrane thickening and loss of intercellular junction proteins result in DME.

Biochemical effects of diabetes

Four pathways have been proposed as the mechanism of microvascular damage as a result of hyperglycemia. These are: (1) polyol pathway (Aldose reductase pathway); (2) advanced glycation end product formation; (3) protein Kinase C activation; and (4) hexosamine pathway.

Until recently, these four pathways were thought to operate separately to form vascular damage. But all these pathways are shown to operate by increasing superoxide formation by the mitochondria and increased superoxide levels play the central role in the combined theory of diabetic retinopathy mechanism[12].

Growth factors and inflamation

Vascular endothelial growth factor (VEGF) is a growth factor that regulates embryologic vasculogenesis and pathologic angiogenesis by stimulating endothelial cell migration and proliferation and increasing survival. Among different members of the VEGF family, VEGF-A plays the key role in ocular angiogenesis and vascular permeability. VEGF-A has 9 isoforms, VEGF-A165 being mostly involved in ocular pathologies[13-15]. VEGF causes DME by the stimulation of the development of neovascularization that are devoid of tight junctions between the endothelial cells[16]. In addition, VEGF has a proinflamatory effect by causing increase in ICAM-1 and VCAM-2 resulting in stimulation of leukocyte chemotaxis and adhesion.

One VEGF family member that has become an important treatment target is Placental Growth Factor (PlGF) which is first isolated from the placental tissue. It causes DME by causing damage to intercellular tight junctions on vascular wall and retinal pigment epithelium. Tissue hypoxia and insulin stimulates PlGF formation which causes subretinal fluid accumulation and increase in retinal edema[17].

There are many evidence that show inflammation plays a role in diabetic retinopathy and DME. The mechanism of intravitreal corticosteroids in decreasing macular edema has not been fully understood but it supports the hypothesis that inflammation is part of the DME process.

The blood retinal barrier does not allow passage of leucocytes under normal conditions. In DM, leucocytes produce toxic superoxide radicals and proteolytic enzymes that weaken the intercellular tight junctions and denature extracellular matrix proteins. This leads to vascular leakage and edema. Leucocytes become rigid and bind strongly to endothelial cells. Combined with rigid erythrocytes and thrombocytes, these leucocytes also cause vascular occlusion. This causes focal retinal ischemia and hypoxia which further leads to increase in inflammatory reaction[18-20].

There are many inflammatory mediators that have been shown to increase in vitreus and systemic circulation in case of diabetes mellitus and diabetic retinopathy. Most studied mediators are tomur necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and intercellular adhesion molecule-1 (ICAM-1). TNF-α is a proinflammatory cytokine and is thought to serve by increasing leucostasis and is related with VEGF and ICAM-1 levels[21]. ICAM-1 is an intracellular protein that is required for the adhesion of leucocytes to endothelial cells. ICAM levels increase with VEGF stimulation and AGE (Advanced glycation products- ileri glukozilasyon ürünleri) products. This also exerts its effect by aiding leucostasis[22]. IL-6 is shown to increase VEGF expression and causes edema by increasing vascular permeability[23,24].

Other factors

Matrix metalloproteinases are cytokines that increase locally with advanced glycation end products, reactive oxygen and direct effects of hyperglycemia. Under normal conditions, they play role in extracellular matrix formation, repair and angiogenesis. They cause protein degradation and weakening of intercellular tight junctions which lead to increase in vascular permeability[25].

Type 1 carbonic anhydrase enzyme has been shown in choroidal endothelium and retina pigment epithelium[26]. CA causes a more profound increase in vascular permeability when compared to VEGF. CA inhibitors are used to treat macular edema caused by other pathologies in which these are thought to inhibit CA in retinal pigment epithelial cells resulting in increased absorbtion of extracellular fluid. But DME patients do not respond well to CA inhibitors. RPE is presumed to be damaged in DM or the abnormal amount of extracellular fluid exceeds the limits of RPE[26-28].

Hypertension is a known risk factor in development and progression of diabetic retinopathy. Angiotensin 2 (Ag-2) increases VEGF and related vascular permeability. Ag-2 is shown to cause pericyte migration and hypertrophy. Angiotensin converting enzyme receptors are found on endothelium, choroid and pericytes. ACE inhibitors decrease blood pressure as well as decreasing retinal blood flow. ACE inhibitors are shown to decrease development of DR in type 1 DM but does not seem to have effect on progression and DR development in type 2 DM patients[22,29,30].

CONCLUSION

In conclusion, as a major cause of visual loss in diabetic patients the pathogenesis of DME is complex, and a variety of factors and biochemical pathways are involved, which provides an opportunity for the development of a number of therapeutic modalities to treat the condition.

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MINIREVIEWS

Predictors of visual outcome in traumatic cataract

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Abstract

Traumatic cataract resulting from open- or closed-globe ocular trauma is one of the most common causes of blindness. Visual outcome is unpredictable because this is not determined solely by the lens. There is a lack of a standard classification, investigations, and treatment guidelines related to the outcome, with considerable debate regarding predictive models. We review the predictors of visual outcome following surgical treatment of traumatic cataracts, which may act as a guide to clinicians.

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Key words: Traumatic cataract; Visual outcome; Birmingham Eye Trauma Terminology System; Ocular trauma score; Morphology of traumatic cataract; Open globe injuries; Classification of ocular trauma; controversy; Pediatric ocular trauma

Core tip: Visual outcome of traumatic cataract is controversial and confusing as it is not only the lens which decides prognosis, but many other factors also responsible. We have tried to address predictors which may forecast visual outcome in case of traumatic cataract.

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INTRODUCTION

Ocular trauma can induce cataract formation[1-6]. The methods used to evaluate the visual outcome in eyes managed for traumatic and senile cataracts are similar; however, the damage to other ocular tissues resulting from trauma may additionally compromise the visual gain following surgery. Therefore, the visual outcome may differ depending upon co morbidities. Ocular trauma remains a controversial topic and the debate over management strategies continues. The international classification of ocular trauma proposed almost 15 years ago requires re-evaluation and should be more robust in terms of predicting the outcome of open-globe injury (OGI)[7].

The introduction of the Birmingham Eye Trauma Terminology System (BETTS) has standardized ocular trauma documentation[8]. Consequently, visual outcomes following traumatic cataract surgery and the determinants predicting the outcome can be investigated with respect to the BETTS category[8,9]. Although visual outcomes of traumatic cataracts have been reported, most studies involved only small populations or were case studies.

The timing of cataract surgery and intraocular lens (IOL) implantation in trauma continues to be debated worldwide. A number of issues regarding the management of traumatic cataract remain unresolved. The high risk of amblyopia and intraocular inflammation as well as strong vitreoretinal adhesions in the pediatric age group require management based on different principles. Prospective, controlled clinical studies of OGI are not possible. This article reviews pertinent data regarding these management issues and controversies, and provides recommendations for treatment based on the available published data and the authors' personal experience. Blindness due to injury is a social and economical burden on society and the individual[6,7,9].

This study was performed with the approval of the

Table 1 Factors effecting visual outcome

Variable	*P* value
Socio-economic status	0.308
Age	0.020
Sex	0.600
Hospital entry	0.010
Habitat	0.431
Previous treatment	0.068
Object causing the injury	0.103
Activity during injury	0.340
Preoperative vision	0.000
Morphology	0.015
Surgical technique	0.000
Primary posterior capsulotomy and vitrectomy	0.001
Time interval between injury and intervention	0.030
Lens implant	0.000
Number of surgeries	0.125
Type of injury (BETTS)	0.000
Type of injury (BETTS subgroup)	0.007
Relative afferent pupillary defect	
Ocular trauma score	0.000
Infection	0.000

BETTS: Birmingham Eye Trauma Terminology System.

Hospital Ethical Committee and complies with the tenets of the Declaration of Helsinki. Written consent in the local language was obtained for the use of the information in this article.

EPIDEMIOLOGY AND INCIDENCE

The incidence, based mainly on retrospective studies and eye injury registries, varies in different regions of world. Incidence variability also arises because of different demographic conditions, including age, sex, environment, and socio-economical conditions[4]. The incidence of traumatic cataract also varies within the pediatric age group[4-6,10,11].

It is imperative that surgeons are aware that traumatic cataract is not a senile cataract. The injury is rarely limited to the lens, but may also be associated with the zonules, posterior capsule, and posterior segment. A patient with traumatic cataract should be informed of the potential visual outcome and the high risk of intraoperative complications[12-19].

It is important to be able to predict visual outcome during the pre-treatment examination as prognosis is to be known to clinician as well as patient. The influence of different variables has been investigated, which we review here with respect to the final visual outcome[20-26].

THE VARIABLES INVESTIGATED AND THEIR SIGNIFICANCE REGARDING THE FINAL VISUAL OUTCOME

Socio-economic factors

Life style, activities, and a lack of protective devices in those of the lower socio-economic group in developing countries make them more vulnerable to ocular injuries; however, visual outcome did not differ with respect to socio-economic factors (Table 1)[1-3].

Age

Younger people are more prone to ocular injuries. The age at intervention has a significant effect, with a better visual outcome achieved in the early age group. It is evident from almost all studies that younger patients respond well to treatment except children under age of 5 who are prone to develop amblyopia.

SPECIAL CONSIDERATION OF TRAUMATIC CATARACT IN THE PEDIATRIC AGE GROUP

Incidence: The incidence varied among studies, most of which were retrospective and involved small databases. Studies on traumatic cataracts in children reported incidences of 25% in southern India, and 12% and 46% in Western India[4-6].

Challenges in children with traumatic cataract include amblyopia, a tendency for inflammation, synechiae and secondary cataract[20]. Children account for approximately one-third of all serious eye injuries[22]. Despite this, the classification and scoring systems in pediatric trauma are based on those developed for adults[22]. The debate over the position of zones Ⅱ and Ⅲ is even more pronounced in pediatric trauma. During the first 5 years the length of the pars plana changes rapidly from approximately 1.8 mm in neonates to 3 mm by 1 year of age, and attains 5 mm at 5 years of age[23,24]. Therefore, pediatric trauma assessment for research purposes is liable to inaccuracy, depending on how the injury is classified.

Children and younger patients exhibit stronger adherence between the posterior capsule and the anterior vitreous centrally; furthermore, the central vitreous is anatomically connected to the peripheral retina at the vitreous base[17]. Any traction on the anterior vitreous face is transmitted to the retina, and the younger the patient, the greater the risk. Additionally, children are at risk of amblyopia. In younger children, a surgeon may resort to a single-step procedure and perform lens extraction, IOL implantation and, if required, anterior vitrectomy for an optimal outcome[25-30]. Primary IOL implantation not only prevents amblyopia but also synechiae formation, which can close the lens capsule by the time secondary IOL implantation is due to be performed[31-33].

Although the management of trauma in children has many similarities to that in adults, striking differences also exist. Foremost is that adults have reached visual maturity, whereas amblyopia is a major contributor to poor outcomes in children, especially in under 5 year olds. The worst outcomes reported were that < 50% of the children with an OGI achieved good vision and amblyopia was a major confounding factor[31-33]. To achieve a clear visual axis following globe repair when treating children with OGI, this must be accompanied by accurate refraction and aggressive patching therapy to improve the visu-

al outcome[34]. A further difference is that a simple examination can prove difficult in a child, especially during the early stages after trauma, resulting in the requirement for general anesthesia or sedation for proper assessment. The involvement of a pediatric ophthalmologist and access to pediatric facilities is therefore essential for ultimate management.

Optical rehabilitation is important because an IOL is not implanted in all cases[21]. Orthoptic treatment following optical correction, including patching and monitoring of visual regain, is vital because amblyopia is an important factor[21].

In conclusion, children with an OGI cannot simply be treated as small adults. Patient age and the effects of amblyopia should be included as additional negative prognostic factors.

Sex

Generally, males are more affected by injuries because of greater participation in outdoor activities; however, no significant difference was found in visual outcome according to sex.

Hospital attendance

Patient hospital attendance has had a significant effect on visual outcome (Table 1)[2,4,34-40]. Patients attend a hospital either by self reporting or *via* outreach activities, including mobile diagnostic camps and school screening. Patients who have attended an outreach program usually present late; thus morphological changes and visual outcome differ.

Habitat

Ocular injuries are more common in rural areas because of the type of related domestic and professional activities[2,4,39,40]. However, the visual outcome did not differ significantly in relation to the habitat.

Previous treatment

The number of patients who received previous treatment depended upon awareness and the availability of services. Past treatment did not have a significant effect on the final visual outcome[39,40].

Object causing the injury

The object responsible for an injury varies according to geographical and socio-economic status, with a marked variation in the United States Eye Injury Register and reports from other sources[2,4,39]. However, there was no significant difference with respect to the visual outcome.

Activity during injury

The type of activity during injury also varies according to geographical and socio-economic status, as indicated by the United States Eye Injury Registry and reports from other sources[2,4], although no significant difference was found regarding visual outcome[39,40].

Preoperative visual acuity of no light perception and poor visual prognosis

Visual acuity can be profoundly impaired, even to the extent of no light perception (NLP), in the presence of significant media opacity (*e.g.*, corneal edema, hyphema, cataract, dense vitreous hemorrhage), retinal detachment, associated subretinal or subhyaloid hemorrhage, hemorrhagic choroids, and even psychological factors (*e.g.*, hysteria). The assessment of light perception is a subjective measurement and not a fool-proof test in the presence of severe media opacity secondary to dense vitreous hemorrhage, traumatic cataract, dense hyphema, or corneal edema. Even with the bright light of an indirect ophthalmoscope, the assessment of light perception can give a false impression of NLP[38]. Ultrasonography is useful in assessing the posterior segment in eyes with media opacity, and to differentiate between retinal detachment and vitreous hemorrhage[38]. However, when using this methodology it is sometimes difficult to differentiate a detached retina from blood clots in the vitreous cavity and membranes[38]. Before deciding on enucleation in NLP patients, reversible causes of vision loss should be excluded, including psychological factors[38]. Even when enucleation appears inevitable, the ophthalmologist should still discuss the possible options with the patient before making a final decision. Primary enucleation of severely traumatized eyes with NLP is controversial due to the risk of sympathetic ophthalmia. Sympathetic ophthalmia with the potential for bilateral blindness is a relative indication for enucleation of an injured eye. Therefore, primary surgical repair should not necessarily be discounted because of the risk of sympathetic ophthalmia in eyes with NLP. Currently, most surgeons recommend a globe-salvaging procedure for eyes with severe trauma with NLP vision at initial presentation.

The age in children at which IOL insertion and rehabilitation of aphakia can be undertaken remains under debate.

Morphology of traumatic cataract

There is no standard morphological classification. Attempts at grading have been made, but these are arbitrary[12]. The morphology of traumatic cataract depends mainly upon the type of injury and the time interval between the injury and intervention.

Based on lenticular opacity, cataracts were classified as: total (Figure 1); white soft with soft material floating in the anterior chamber with broken anterior capsule (Figure 2); membranous, in which both capsules were fused with little or no cortical material (Figure 3); and rosette (Figure 4). A cataract was defined as total when no clear lens matter was observed between the capsule and nucleus. For a membranous cataract the capsule and organized matter were fused and formed a membrane of varying density. A cataract was considered to be white soft when loose cortical material was found in the anterior chamber together with a ruptured lens capsule. A lens with a rosette pattern of opacity was classified as

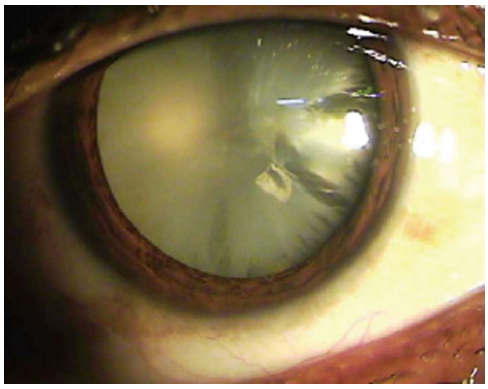

Figure 1 When no clear lens matter was visible between the capsule and the nucleus, the cataract was defined as a total cataract.

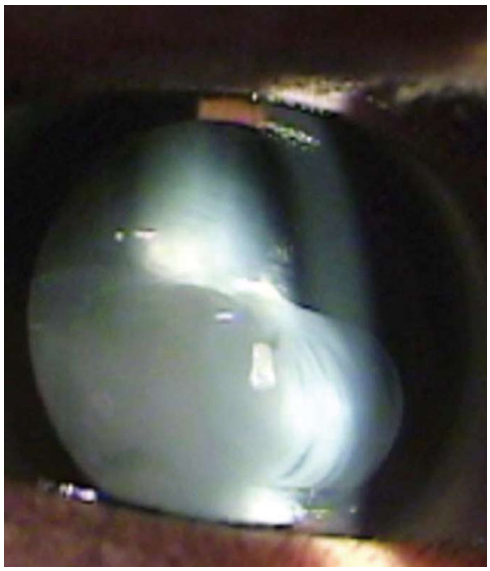

Figure 2 When loose cortical material was found in the anterior chamber together with a ruptured lens capsule, the cataract was defined as a white soft cataract.

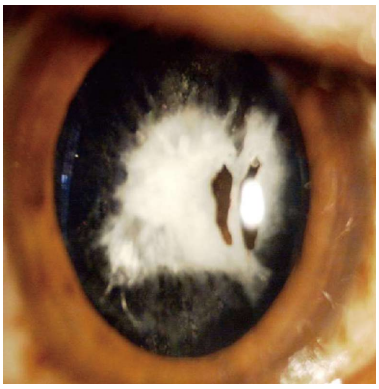

Figure 3 When the capsule and organised matter were fused and formed a membrane of varying density, the cataract was defined as a membranous cataract.

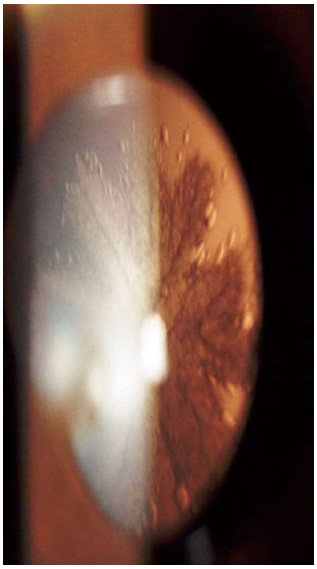

Figure 4 A lens with a rosette pattern of opacity was classified as a rosette type cataract.

a rosette cataract. One study proposed that all cataract cases could be assigned to these groups[13].

Management and surgical approaches to traumatic cataract

The choice of surgery in adults in whom amblyopia is not an issue is governed by the surgeon's own preferences and to a certain extent by the status of the cataractous lens. If the anterior capsule is significantly disrupted and there is free floating lens matter in the anterior chamber, the surgeon may be justified in primary cataract extraction with or without IOL implantation (Figure 3).

Eyes with a lens vitreous admixture should be considered for combined cataract extraction with limited anterior vitrectomy. Judicious use of a vitrector and not an aspirator should be made while removing vitreous admixture in the ruptured lens matter (Figure 4). Any traction on the vitreous may result in inadvertent retinal breaks[14]. When there is additional injury to the posterior segment, early pars plana lensectomy and vitrectomy by a posterior segment specialist is warranted[14]. In eyes with an intact anterior capsule and total traumatic cataract, a second-sitting cataract extraction with IOL implantation should be the best and safest approach for optimal visual outcome[17,18].

Wherever possible, a multistep procedure after control of inflammation, with adequate corneal clarity and an appropriate IOL power calculation, should be adopted[18,19]. It remains debated whether an anterior or posterior surgical approach via the pars plana route should be performed.

The following forms of surgical approach may be used, according to morphology: (1) unimanual or bimanual aspiration; (2) lensectomy/membranectomy using the limbal or pars plana approach and insertion of the lens in the sulcus; and (3) phacoemulcification or small-incision cataract surgery when the nucleus is harder[13].

Primary posterior capsulotomy

Determination of the correct IOL power prior to surgery

may be difficult, if not impossible, for a variety of reasons. Often the other eye serves as a guide, and inflammatory debris can settle on the IOL surface, cleansing of which may require postoperative yttrium-aluminum-garnet laser treatment or even surgery. In addition, the edge of the IOL will interfere with the surgeon's visualization of the peripheral retina should subsequent development of proliferative vitreoretinopathy necessitate vitrectomy[35]. There has been considerable debate over the use of primary posterior capsulotomy[39-41].

Primary posterior capsulotomy and vitrectomy in traumatic cataract have proved to be positive outcome predictors[39,40]. It was found that condensation of the anterior vitreous in severe inflammation was a positive outcome predictor in nonrandomized studies, while a randomized controlled trial suggested that this was a positive predictor.

Timing of intervention

The timing of cataract extraction and IOL implantation has been discussed extensively. Because evidence supports both primary and secondary cataract extractions, a number of crucial factors should be considered before making a decision. Cataract extraction together with primary wound repair may have distinct advantages, including controlling inflammation, however, this may raise intraocular pressure because of soft lens matter in the anterior chamber[13]. Secondary advantages include the direct visualization of the posterior segment and optic nerve[14]. Similarly, in pediatric patients the removal of a media opacity may be crucial to prevent vision-deprivation amblyopia. In patients with a lens vitreous admixture, this is a potent stimulator for further proliferative vitreoretinopathy and may also result in traction on the retina; hence primary extraction of the lens and vitreous is imperative in such patients [35,36]. Minor advantages of primary lens removal are the patient's convenience and possibly cost effectiveness[14].

Proponents of second-sitting cataract extraction recommend effective control of intraocular inflammation, good media clarity, and a stable wound before considering traumatic cataract extraction[14,39]. On adequate control of inflammation, IOL implantation at second-stage cataract extraction may be associated with a better outcome[14,39]. An IOL power calculation is appropriate when IOL implantation is planned for a second sitting[18,35].

Current data suggest that improved visual outcome results from intervention at 2-30 d[36]. Awareness of several details is necessary before embarking on primary or delayed cataract extraction with IOL implantation. These include the age of the patient, the expertise of the surgeon and assisting staff, the infrastructure available, and the status of the cataractous lens and the lens vitreous admixture, which will act as a guide to the surgeon in planning the surgery.

The ophthalmologist must not subject a patient to half-completed or compromised surgery because of a lack of expertise or proper infrastructure. If the facility is not equipped to provide the surgeon after hours with the full range of equipment, instruments, and material together with a full and knowledgeable staff, it is preferable not to contemplate primary lens removal. In most hospitals globally when an OGI is seen after hours, the state-of-the-art facilities necessary to attempt cataract extraction and IOL implantation are not normally available.

Lens implant

Lens implantation is an important stage in traumatic cataract surgery. A primary implant at the time of cataract extraction or a secondary implant during a second sitting is important for optical rehabilitation[39,40]. The lens implant may be placed in the capsule or sulcus, be iris supported, or involve scleral fixation depending upon the extent of the damage. Lens implants help in optical rehabilitation and the prevention of amblyopia in children. Lens insertion makes a significant difference to visual outcome.

Number of surgeries

Ocular injuries may cause damage to multiple ocular structures. It may therefore be impossible to treat all of the tissues in one session; thus a number of surgeries may be required to complete surgical management. Corneal/scleral wound repair, cataract extraction, lens implant, membranectomy, or vitrectomy may be performed at different stages[39,40]. Various studies reported that the number of surgeries did not have a significant effect on the final visual outcome.

Type of injury

The type of injury may influence visual outcome. Reports have suggested that OGI has a better outcome, whereas the opposite was true for penetrative injury[38-40]. Influences open globe of BETTS as a predictive factor (Table 1)[39,40]. When compared to the open-globe subgroups, cataract caused by penetrating injury had a better outcome whereas globe rupture had a poorer outcome[39-41].

CLINICAL CONDITIONS THAT MAY PREDICT PROGNOSIS

Relative afferent pupillary defect

There is sufficient evidence to suggest that relative afferent pupillary defect (RAPD) may produce false positives with regard to damage to the optic nerve or retina in the presence of severe hyphema or subretinal vitreous hemorrhage, which may resolve after resorption or removal of the hemorrhage[41-44]. Therefore, RAPD alone is a poor prognostic factor, it may be inappropriate, and there is the possibility of reversal[37]. Therefore, RAPD should be weighted equally with other preoperative variables following ocular trauma.

Predictive methods

The ocular trauma score (OTS) was developed to provide more accurate information regarding the visual prognosis. However, it is unclear whether children were included

in the databases of the over 2500 serious ocular injuries from which the method was formulated[45-47]. Two reports from India validated OTS using 787 cases of traumatic cataract[48,49].

Two important factors in calculating the OTS, initial visual acuity and RAPD, are difficult to obtain for children after trauma, especially those in the younger age group, rendering the OTS inaccurate or even unusable. Two groups recently assessed the value of the OTS in pediatric patients aged from 2 years, coming to opposite conclusions, thus adding to the controversy[50,51]. A new pediatric OTS that aimed to refine prognostic accuracy in children in whom the initial vision is not accurate was published recently[52]. As in many other studies on pediatric trauma, it lacks the statistical power of the OTS because of its relatively small population size, and its predictive power remains untested. The OTS appeared be a valid predictor of visual outcome in children following surgery in a study of 354 pediatric traumatic cataracts[49]. Regression tree analysis has also been used, but has not been validated[53,54].

Infection following OGI

Many studies have reported infection and endophthalmitis following OGIs[56-70]. Intraocular infection is also common with a retained intraocular foreign body[70-72]. The absence of infection following injuries caused by a wooden stick when using plants with antimicrobial and antifungal properties has been reported[73-79].

CONCLUSION

Despite the advances in state-of-the-art surgery and understanding ocular trauma, a range of unresolved, controversial issues remain in the management and treatment of OGIs. During the last two decades all of these issues have been addressed and real progress has been made in many aspects of the definitive management of traumatic cataracts.

The timing of the intervention in traumatic cataract appears to be a never-ending debate. "Sooner the better" was the traditional view; however, an alternative view is that a better outcome results from intervention between 3-30 d. Although a controlled, prospective clinical trial would be the ideal, no two ocular trauma cases are alike, and confounding factors can affect the final outcome.

A morphological assessment may be used to guide management. The age at intervention and laterality play important roles as predictors of visual outcome[21,40,49]. The accuracy of predictive models varies between adult and pediatric traumatic-cataract cases.

Controlling for the significant differences that occur among individual injuries is difficult. This makes the independent assessment of potential risk factors and treatment variances for visual and anatomical outcome difficult. Current management is based on the surgeon's experience, and will continue to be based on a retrospective review of accumulated data and the personal preferences of the treating ophthalmologist in OGI. These types of management problems are dealt with on a case-by-case basis, and even the most experienced ophthalmologists will at some time find themselves in a dilemma regarding the strategic planning of ocular trauma management of OGI. This review has attempted to provide a comprehensive overview of most of the controversies related to the management of OGI, and has presented our preferred guidelines. This should aid ophthalmologists in patient counseling and the process of making decisions regarding the management of OGIs involving the anterior or posterior segment.

In summary, the vast majority of ophthalmologists who encounter a traumatic cataract have sufficient experience in lens extraction and IOL implantation in the non-traumatic setting. What every ophthalmologist must accept is that an injured lens requires many individualized, conscious decisions regarding what to do, when to do it, and how to achieve the best possible outcome.

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MINIREVIEWS

Donor cornea quality used for penetrating keratoplasty *vs* deep anterior lamellar keratoplasty

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Abstract

Deep anterior lamellar keratoplasty (DALK) has recently been introduced as an alternative procedure to penetrating keratoplasty (PK) for corneal pathologies not affecting the corneal endothelium. DALK does not rely on donor endothelium and requires less rigid criteria for donor corneal tissue quality. Therefore, DALK makes it possible to use donor corneas deemed unsuitable for PK. Furthermore, lamellar keratoplasty allows acellular corneal tissue to be transplanted. As a result, long-term preservation techniques are being revisited to increase the availability of donor corneas and subsequently alleviate constraints of availability, cost, storage, and transportation in many countries. The recent alterations in corneal transplantation techniques and hence the type of donor cornea tissues used for each technique, may require corneal surgeons and eye banks to reevaluate their selection criteria. The purpose of this systematic review is to present an updated analysis on the type and quality of donor corneas used for PK and DALK, assess the influence of donor and eye bank factors on the quality of donor corneas, and determine whether any of these donor factors affect clinical outcomes, complications, and graft survivals.

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Key words: Corneal transplantation; Penetrating keratoplasty; Full-thickness keratoplasty; Deep anterior lamellar keratoplasty; Deep lamellar keratoplasty; Maximum depth anterior lamellar keratoplasty; Donor corneal quality; Graft quality

Core tip: Deep anterior lamellar keratoplasty (DALK) is recently used for treating corneal diseases not affecting the corneal endothelium. This makes it possible to use donor tissue with poor endothelium. Furthermore, DALK allows acellular corneal tissue to be used and long-term preservation techniques are being considered as a method for donor storage. The recent alterations may require eye banks and corneal surgeons to reassess their selection criteria to ensure donor grafts which are inappropriate for penetrating keratoplasty because of low endothelial cell count can be safely used for DALK.

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INTRODUCTION

Penetrating keratoplasty (PK) is a surgical technique in which the full thickness of the recipient cornea is replaced by donor tissue. Deep anterior lamellar keratoplasty (DALK) is intended to selectively replace the abnormal stroma while preserving the recipient's endothelium in place[1]. Therefore, DALK can eliminate the risk of

endothelial graft rejection and has minimal detrimental effect on endothelial cell density[2]. Some investigators report that visual acuity and refractive error following DALK can be similar to those following PK[3-6].

The recent alterations in corneal transplantation techniques and consequently the type of donor cornea tissues employed for each technique may require corneal surgeons and eye banks to reevaluate their donor selection criteria.

Controversy exists regarding the donor corneal tissue quality used for each transplantation technique. Donor factors such as age, local and systemic diseases, cause of death, and traumatic damages or surgical procedures as well as the storage factors (mainly method of storing, time between death and preservation, and duration of tissue preservation) can influence the final quality of the corneas. When indicated for optical purposes, PK surgeons prefer transplanting donor cornea tissues with quality ranging from good to very good to excellent to provide adequate endothelial cells for a lifelong period. Since the introduction of DALK, many surgeons have been accepting donor corneas with lower quality compared with PK. DALK does not rely on quality of the donor endothelium and requires less strict criteria for donor selection[7]. This feature is imperative in increasing the availability of corneal grafts in regions where there is shortage of donor corneas[7].

The purpose of this systematic review is to present an updated analysis on the type and quality of donor corneas used for PK and DALK, to assess the influence of donor and eye bank factors on the quality of donor corneas, and furthermore to determine whether any of these donor factors affect clinical outcomes, complications, and graft survival.

RESEARCH

Questions for assessment

The objective of this assessment is to address the following questions: (1) what type and quality of donors are used for PK and DALK? (2) What is the influence of donor and eye bank factors on the appropriateness of corneal grafts for transplantation [endothelial cell density (ECD)] and graft quality)? (3) Do donor and eye bank variables affect clinical outcomes, complications, and graft survivals following PK and DALK?

Description of evidence

A search of the peer reviewed English literature was performed using the PubMed database between January 14, 2014 and April 15, 2014. Article reference lists were also reviewed to identify relevant articles. Keywords used in the search included the MeSH heading "corneal transplantation" combined with text words "deep anterior lamellar keratoplasty" or "DALK" or "deep lamellar keratoplasty" or "maximum depth anterior lamellar keratoplasty" and "penetrating keratoplasty" or "PK" (MeSH and text) or "full-thickness keratoplasty" accompanied with "donor quality" or "graft quality".

Then, a group of methodologists assigned a level of evidence rating to each article. A level Ⅰ rating was assigned to well-designed randomized clinical trials; a level Ⅱ rating was assigned to poor-quality randomized clinical trials or well-designed case-control and cohort studies; and finally a level Ⅲ rating was assigned to case reports and poor-quality case-control or cohort studies.

In order to evaluate the minimal endothelial cell count limits, the upper and lower limits of donor age, maximal time intervals from death, enucleation or excision to preservation, and maximal storage time deemed suitable for corneal transplantation, studies on the characteristics of donor corneas used for transplantation were reviewed.

The author assessed the 61 citations and selected 48 articles that potentially or definitely met the inclusion criteria. The full text of these 48 articles was obtained for further evaluation.

Nine studies were prospective, double-masked clinical trials (level Ⅰ) reported by the Cornea Donor Study[8-16]. Four studies were prospective non-randomized trials (level Ⅱ)[17-20]. The remaining 35 articles were comparative or non-comparative case series and were rated as level Ⅲ evidence[21-47].

Type and quality of donors used for PK and DALK

Assigned corneas for PK with quality ranging from good to excellent had the following characteristics: donor age varied from 1 to 96 years[9,10,19-23,46]; endothelial cell density varied from 2000 to ⩾ 3000 cells/mm^2[9,10,18,24]; death-to-preservation time was between 45 min and 22.3 h[19,22,23,25]; maximum storage time was 14 d in cool-storage media and 4 wk in organ culture[19-21].

In contrast to penetrating keratoplasty, donors with quality ranging from fair to excellent were employed for DALK[26,27]. Furthermore, long-term preserved donor tissues completely devoid of cells were also transplanted[28-31]. One DALK study used donor cornea tissues with age between 12 and 72 years, graft rating from fair to excellent, ECD between 1128 and 4255 cells/mm^2, death-to-preservation time up to 56 h, and storage time up to 13 d in Optisol medium (-4 ℃)[26]. Another DALK study used donors with the following features: age between 28 and 88 years, ECD between 100 and 3300 cells/mm^2, and storage time up to 35 d in organ culture medium (31 ℃)[27].

Long-term preserved corneas with mean storage time between 2.7 and 9.6 mo were also used for DALK by some surgeons[28-31]. The majority of studies used lyophilization or chemical agents to dehydrate corneas before cryopreservation[28-30]. One study, however, employed cryopreservation without dehydration before freezing[31].

Effect of donor and eye bank variables on endothelial cell density and graft quality

Most studies that evaluated effects of donor characteristics and eye bank variables on graft quality and ECD concluded that the age of donor and time interval in organ culture were the main variables influencing the quality of endothelium. Gavrilov *et al*[32] reported that the rate

of organ-cultured corneas which were inappropriate for PK as a result of inadequate endothelium increased from 13% in donors < 40 years to 32% in donors > 80 years. The Cornea Donor Study revealed a negative correlation between donor age and ECD[16].

Armitage *et al*[24] revealed that the age of donor and preservation time in organ culture were the main variables which could affect endothelial suitability for PK. The odd of ECD less than 2500 cells/mm^2 was increased with longer preservation time and increasing donor age. Increasing time interval from enucleation to corneoscleral disc excision also increased the likelihood of ECD less than 2500 cells/mm^2 but the overall impact was small and significant only for a time interval greater than 18 h[24].

Grabska-Liberek *et al*[33] found that the rating of the morphological state of corneas suitable for PK depended mostly on the time between death and preservation, donor's age, cause of death and duration of preservation. The overall rating of tissues obtained in a very short time after death (to 5 h) was higher (excellent and very good) compared with corneas removed 8-12 h after the donor's death. An increasing percentage of endothelial cell loss was observed after 7 d of preservation independent of other factors[33].

One study found that initial ECD was lower and elimination for low ECD was more frequent in donors aged 85 years and over, compared to younger donors[17]. However, after storage in organ culture, very old corneas lost fewer endothelial cells than younger ones resulting in ECD which did not differ at the end of storage[17].

One study measured endothelial cell loss during preservation in organ culture[25]. The donor's gender, age, cause of death, and postmortem interval had no significant correlation with the percentage of endothelial cell loss. However, the preservation time demonstrated a significant correlation with a loss of 0.07% for each day of preservation[25].

Additionally, the combined effects of cause of death and donor age on ECD were evaluated. It was identified that chronic and long-lasting, severe diseases like cancer reduced ECD to a greater extent as compared to diseases causing a more rapid death. This negative impact of chronic diseases was aggravated by the general reduction in ECD observed with increasing age[34].

Effect of donor and eye bank variables on clinical outcomes, complications, and graft survivals following PK

Five studies investigated the effect of donor and eye-bank variables on epithelium-related problems following PK[19,23,35-37]. Death-to-preservation time and total storage time were significantly associated with an increased prevalence of epithelial defects on day 1 or hurricane and filamentary keratopathy[19,23]. Kim *et al*[35] outlined that the degree of epithelial defect had a statistically significant association with the time interval from preservation to surgery. Borderie *et al*[36] reported that death-to-storage time, storage time, and deswelling time significantly influenced the graft reepithelialization time in univariate analysis. In multiple regression however, none of the donor variables significantly influenced the graft reepithelialization time. As for the surface keratopathy 1 wk following PK, Mannis *et al*[37] observed no correlation between this complication and donor age, death-to-preservation time, preservation-to-surgery time, and the donor epithelial status.

Another widely investigated correlation was the effect of donor and eye-bank variables on postoperative ECD which yielded contradicting results. Langenbucher *et al*[21] reported no significant association between the annual endothelial cell loss and the donor age as well as postmortem interval. However, the storage time had a statistically significant correlation with the annual endothelial cell loss. Parekh *et al*[25] reported postmortem interval ≥ 10 h tends to have a higher percentage of endothelial cell loss than < 10 h of interval at both 1 year and 3 years postoperatively.

Postoperative higher ECD values were significantly associated with higher baseline ECD and younger donor age in one study[9]. When the follow-up period was extended to 10 years, the study group observed that the donor age influenced ECD, although this finding was primarily influenced by a small group of the youngest donors (12 to < 34 years of age) that had the least cell loss and the best graft survival[9]. Lass *et al*[11] observed the younger age and female gender of the donor had a significant correlation with higher ECD over time. However, cause of death and time interval from death to preservation or to surgery failed to demonstrate any significant association with changes in ECD during follow-up[11]. One study found a statistically significant negative influence of postmortem time and donor age on chronic loss of endothelial cell density after PK for keratoconus[38].

Two studies reported the effect of donor age on visual outcomes. Gain *et al*[17] found no significant difference between the two groups (donors younger than 85 years and donors aged 85 years and older), in terms of visual acuity and astigmatism. Halliday *et al*[39] found no significant correlation between the time taken to reach a postoperative acuity of 6/12 and the age of donor.

One study reported that donor age, ABO compatibility, and other donor factors were not associated with graft rejection[8]. Younger donor age, however, was found a risk factor for graft rejection (but not for graft failure) by three other studies[17,40,47].

Despite contradictory results of studies evaluating the effect of donor and eye-bank variables on ECD and morphology, the majority of studies showed that donor preservation method and time, donor age, cause of death, and preoperative donor ECD and/or morphometric measures (coefficient of variation and hexagonality) had no influence on overall graft failure[12,13,17,20,22,40,41]. However, one study reported that preoperative risk factors for developing late endothelial failure included low ECD and older donor age[46]. Authors from the Cornea Donor Study observed that grafts from donors aged between 66 and 75 years old that met the eligibility criteria of their study had a 5-year graft survival rate, comparable to grafts from younger donors[10]. However, higher donor

age was significantly associated with lower graft success during a longer follow up period[15].

Effect of donor and eye bank variables on clinical outcomes, complications, and graft survivals following DALK

Borderie *et al*[27] evaluated the effect of donor variables on the result of different anterior lamellar keratoplasty techniques in a heterogeneous group of corneal disorders with normal endothelium. The age of donor was the only factor which influenced visual rehabilitation postoperatively; visual acuity was significantly lower in recipients who received corneas from donors > 80 years[27]. Heindl *et al*[42] did not observe any significant association between donor storage time intervals and visual results one year following DALK. Feizi *et al*[26] observed that graft rating and preservation-to-surgery time had a significant correlation with the presence of graft stromal edema and epithelial defects on postoperative day 1 following DALK. Suture-related complications, graft rejection episodes, graft clarity, visual acuity and refractive outcomes at the final follow-up examination were found to have no correlations with any donor or eye-bank factors[26].

Five studies concluded that long-term cryopreserved donors can provide similar visual results comparable to fresh corneal tissues following DALK[28,29,31,43,44]. Another advantage of long-term preservation of the cornea by lyophilization and chemical glycerin-dehydration is to eliminate cells such as epithelium, keratocytes, and antigen-presenting cells and create the acellular biological materials[28,45]. As such, acellular corneal tissues may significantly reduce or even eliminate the incidence of graft rejection after lamellar keratoplasty[28,29,31]. Complications such as persistent epithelial defects, filamentary keratitis, and suture-related complications were more likely to occur when such a low quality graft was transplanted[31].

There is currently a paucity of evidence for setting an acceptable minimum donor conditions for corneal transplantation, especially for lamellar keratoplasty. According to Eye Bank Association of America standards for human corneal transplantation, minimal endothelial cell count limits, the upper and lower limit of donor age, time intervals from death, enucleation or excision to preservation are left to the discretion of the eye banks[48]. An understanding of the effect of donor variables including age, time interval from death to enucleation and to preservation, storage time, and endothelial cell density both on the quality of donor corneas and on post-transplantation outcomes help to set eye banking standards. To establish the criteria, it is vital to find out the correlation between these donor parameters and the appropriateness of corneas for transplantation as well as between donor parameters and post-transplantation outcomes. The aim of this review, therefore, was to assess the influence of donor and eye bank factors on the graft quality as well as clinical outcomes.

Based on to the results of this review, the minimum ECD for PK is 2000 cells/mm^2 and there is no age limit for donors. Death-to-preservation time up to 24 h is accepted and maximal storage time is 14 d in cool-storage media and 4 wk in organ culture.

Because endothelial cell graft attrition takes place at an accelerated rate[49], a higher initial endothelial cell density of the donor tissue can improve long-term graft survival[9]. Older donor age and longer storage time are more likely to be associated with lower ECD but, as long as the ECD is greater than a given minimum at the time of corneal transplantation, these parameters will have insignificant influence on long-term graft survival. The Cornea Donor Study results indicate that donor age is not an important factor in most penetrating keratoplasties performed for endothelial disease[15]. Therefore, functional and cellular results of PKs are not dramatically influenced by very old donor age and the very elderly should not be deemed off limits for corneal procurement.

The results of this review showed that epithelium-related complications such as filamentary keratitis and persistent epithelial defects correlate with longer death-to-harvest time and longer storage time[19,23,35]. In addition to donor endothelial status, graft corneal surface is a determinant for the success of corneal transplantation in the postoperative period. Although the donor cornea is ultimately resurfaced by the recipient's epithelium, an intact donor epithelium on postoperative day 1 implies a smoother course after corneal transplantation. An instable graft surface can lead to poor visual acuity due to an irregular tear film interface, discomfort, permanent damage to Bowman's layer, sub-epithelial scarring, and even infectious keratitis[19].

DALK has recently been introduced to replace abnormal corneal stroma while preserving the host's healthy endothelium. DALK does not rely on donor endothelial cells and less strict criteria can be used for donor graft quality. Therefore, it increases the availability of donor tissues that do not require high-quality endothelium to be appropriate for PK. However, the use of low quality donors for DALK could cause epithelium-related complications more frequently, besides more edematous alterations of the graft necessitating a closer follow-up immediately after surgery. Apart from that, low quality donors can provide good visual acuity and refractive outcomes with complication rates comparable to those achieved after the use of good quality donors following DALK.

The two main techniques for storing corneas are organ culture and hypothermia[50,51]. Since lamellar corneal transplantation makes it possible to use acellular corneal tissue, long-term preservation methods have emerged as a means to provide a greater availability of corneal tissue to alleviate constraints of availability, cost, storage, and transportation in many countries. The results of several studies indicate that cryopreserved corneal tissues can successfully substitute for fresh grafts in DALK using the big-bubble technique. One advantage of long-term preservation of the cornea is to significantly reduce or even eliminate the incidence of graft rejection. However, complications such as persistent epithelial defects, filamentary keratitis, and suture-related complications are more likely to develop with such low quality grafts making closer

follow-up visits essential immediately after DALK.

CONCLUSION

Although both donor and eye bank variables have effects on the quality of donor corneas, and post-PK outcomes and complications, these effects would be little provided that the minimum selection criteria set by eye banks are respected. DALK makes it possible to transplant corneas with low quality and allows using the long-term methods of storage. Because, epithelial defects and stromal edema are more frequently encountered, closer follow-up visits are required when a low-quality graft is transplanted.

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