Corneal complications of glaucoma surgery

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Purpose of review

Most glaucoma surgery can adversely affect the cornea. This often consists of mild endothelial loss on specular microscopy, but occasionally corneal decompensation may occur. The effect on the cornea also depends on preexisting corneal disease, severity and chronicity of intraocular pressure elevation, prior intraocular procedures and complications. With the exception of aqueous shunts, glaucoma procedures are not known to result in progressive endothelial cell loss.

Recent findings

Corneal problems are most common after aqueous shunts, especially in children, in which tube-endothelial touch is common. However, other corneal effects of glaucoma surgery have also been reported. Antiproliferative drugs have a toxic effect on endothelium that may be reduced by concurrent use of viscoelastics. Subconjunctival mitomycin C injection may cause limbal stem cell deficiency. In combined phacoemulsification and trabeculectomy, a one-site approach induces less endothelial trauma than two sites. Overhanging blebs may induce corneal dissection, and even decompensation. Descemet's membrane detachment has been reported after nonpenetrating glaucoma surgery, although less endothelial loss is induced than after trabeculectomy.

Summary

Corneal complications are commonest in patients with aqueous shunts, and long-term prospective studies of endothelial cell density are required to elucidate the factors that predispose to corneal endothelial cell loss.

Keywords

aqueous shunt, corneal complication, cyclodiode, nonpenetrating glaucoma surgery, trabeculectomy

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Introduction

Improvements in the surgical management of glaucoma and the use of antiproliferative drugs have resulted in better intraocular pressure (IOP) control after glaucoma surgery [1–3]. The safety profile of filtration surgery has also improved since the evolution of guarded from full-thickness procedures, and more recently, to nonpenetrating glaucoma surgery. Recent advances in guarded-filtration procedure have reduced the incidence of complications [4], but despite these improvements, postoperative complications still occur, and corneal endothelial cell loss is more common. Glaucoma itself predisposes to endothelial loss when compared with age-matched controls [5], as does acute angle closure [6]. Corneal edema has also been reported after argon laser iridotomy for narrow angles [7,8]. Eyes that have had a previous attack of angle closure and laser iridotomy are, therefore, at a greater risk of corneal edema. This article highlights the elevated risk of corneal complications in eyes undergoing glaucoma surgery.

The influence of antiproliferatives

The use of 5-fluorouracil (5-FU) and mitomycin C (MMC) have improved the outcome of filtration surgery. The higher risk of severe complications that was initially reported after their introduction such as bleb-related endophthalmitis and hypotony maculopathy are still of concern, but appear to be less common with improved surgical technique. Previous studies have cited greater corneal endothelial cell loss with standard nonantiproliferative trabeculectomy versus controls [9]. Greater endothelial cell loss has also been found in trabeculectomy with antiproliferatives versus standard trabeculectomy [10,11] and also in cases of complicated trabeculectomy, in which iridocorneal touch occurs [12]. Dreyer *et al.* [13] did not find a significant difference in endothelial cell loss between 5-FU and MMC trabeculectomies. Furthermore, in a series of 10 patients with iridocorneal endothelial syndrome who had undergone MMC trabeculectomy, Lanzl *et al.* [14] did not report any worsening of their corneal status postoperatively, although cell density

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measurements were not taken. Severe corneal complications such as regional bullous keratopathy, adjacent to the site of MMC application, have been reported [15]. Although corneal endothelial cytotoxicity has been demonstrated with both 5-FU and MMC *in vitro*, Nuyts *et al.* [16] concluded that the dose and method of application used in practice should not result in significant corneal complications unless there has been inadvertent exposure to the anterior chamber. Shin *et al.* [17] assessed the affectiveness of using sodium hyaluronate (Healon TM; Advanced Medical Optics, Santa Ana, USA) to counteract the cytotoxic effect of MMC on the corneal endothelium. The authors measured corneal endothelial cell density (CED) in two groups of patients undergoing 0.2 mg/ml MMC trabeculectomy. One group had Healon injected into the anterior chamber and the other with balanced salt solution (control). The percentage of CED loss was significantly reduced in the Healon group (−2.2%) compared with controls (−7.7%), and the authors concluded that viscoelastic injection might be protective to corneal endothelium when antiproliferatives are used.

Subconjunctival injection of mitomycin C

Subconjunctival application of antiproliferative drugs is normally carried out by soaking the drug in sponges and placed beneath the conjunctiva for a few minutes close to the surgical site. A disadvantage of this method is delayed conjunctival healing and wound leak that may occur if the drug comes into contact with the conjunctival margin. Sauder and Jonas [18] proposed injecting the antifibrotic drug beneath the conjunctiva at the start of surgery before opening the conjunctiva. The authors injected 0.1–0.2 mg/ml of MMC subconjunctivally in seven patients (seven eyes) undergoing standard trabeculectomy at the start of surgery. Three patients (43%) had marked ocular surface problems that included one corneal thinning and two scleral melts. Although the remaining four patients (57%) did not show an adverse reaction to the injection, the authors concluded that subconjunctival injection of MMC in a dosage of 0.2 mg/ml as an adjunct for trabeculectomy should be avoided because of the potential for severe ocular surface problems.

Phacoemulsification and trabeculectomy

Patients undergoing combined surgical management of cataract and glaucoma can have the two procedures performed via one site or separate sites. There is still no consensus as to which is the superior strategy in terms of long-term IOP control. Previous studies have reported one-site surgery to be safe [19], but it required more postoperative IOP medication than two-site surgery [20]. In an evidence-based review, Jampel *et al.* [21] concluded that there was weak evidence to suggest a 1–2 mmHg IOP advantage in two-site compared with one-site surgery.

Data comparing the degree of CED loss between one-site and two-site approaches are limited. Caprossi *et al.* [19] did not find a significant change in CED with the one-site approach. Buys *et al.* [22••] looked at CED loss and IOP reduction over a 2-year period in a prospective randomized control study. There was a significantly lower cell count at 3 and 12 months in the two-site versus one-site group, but this was no longer significant at 24 months, although the cell counts were still lower in the two-site group (1947 ± 471 cells/mm^2) compared with the one-site group (2147 ± 477 cells/mm^2) ($P = 0.08$). The authors speculated that the temporal incision in the two-site approach might be associated with greater endothelial trauma, whereas the more posterior scleral tunnel incision used in the one-site approach might result in less endothelial damage.

Bleb needling

Postoperative bleb needling with antiproliferatives for failed filtering blebs may be successful in controlling the IOP [23–26], but can also cause serious complications such as choroidal effusion, corneal complications [27–29] and endophthalmitis [30]. In a recent prospective observational study of 81 consecutive patients undergoing bleb needling, Roachford and King [31] reported one case of corneal decompensation in a pseudophakic eye after five needlings, but the authors did not comment on why this might have occurred, and corneal transplantation was subsequently required.

Dissecting bleb

Intracorneal dissection of a drainage bleb and overhanging of the bleb are late complications that often cause dysesthesia. The visual acuity can be affected by bleb-induced astigmatism [32,33,34•]. Surgical management involves blunt dissection of the overhanging bleb from the cornea followed by limbal excision, whereas the dissecting bleb often requires removal and refashioning of the whole bleb. There has been controversy as to whether these are separate entities. A recent case report [34•] with histopathological examination of a dissected bleb demonstrated loose connective tissue between the limbal corneal epithelium and Bowman's layer, suggesting that the bleb was dissecting into cornea.

Nonpenetrating glaucoma surgery

Nonpenetrating glaucoma surgery (NPGS) [35] avoids some of the immediate postoperative complications of trabeculectomy. Descemet's membrane detachment has

been reported in both deep sclerectomy and viscocanalostomy, leading to localized corneal edema [36–38]. Ravinet *et al.* [36] retrospectively reviewed nine eyes, in which Descemet's membrane detachment developed after NPGS. Four eyes that had viscocanalostomy maintained corneal clarity, despite the appearance of Descemet's membrane detachment soon after surgery, whereas five eyes that had deep sclerectomy with collagen implant developed localized edema weeks to months after surgery. Fujimoto *et al.* [37] reported a case of intracorneal hematoma, in addition to Descemet's membrane detachment following viscocanalostomy. In a series of 15 patients who underwent combined phacotrabeculotomy with deep sclerectomy, Lüke *et al.* [39•] did not report any cases of Descemet's membrane detachment.

Trabeculectomy versus deep sclerectomy

Arnavielle *et al.* [40••] compared CED loss after trabeculectomy with deep sclerectomy. Cell density was measured in the central and superior cornea with noncontact specular microscopy preoperatively and at 3 months and 1 year after surgery. The cases comprised single trabeculectomy ($n = 18$), single sclerectomy ($n = 14$), combined procedures of phacoemulsification (PHACO) with trabeculectomy ($n = 11$) and PHACO with sclerectomy ($n = 19$). A significant difference in CED loss was found between single trabeculectomy (9.6%) and single sclerectomy (4.5%) after 1 year. The degree of CED loss was also greater in combined PHACO with trabeculectomy (12.3%) versus PHACO with sclerectomy (7.8%). The authors suggested that CED loss was greater with trabeculectomy than sclerectomy, but further clinical studies with longer follow-up are required.

Aqueous shunts

Not only has aqueous shunt implantation increased significantly in the past 10 years, but also the threshold for implantation has lowered and the indications broadened. This is partly because of a better safety profile resulting from increased experience in shunt implantation [41••] and also evidence of better efficacy than previously perceived [42]. Corneal complications after shunt implantation have been reported to occur in 8–29% of patients [42]. However, McDermot *et al.* [43] did not find a significant progressive CED loss in patients undergoing uncomplicated Molteno drainage device (Molteno Opthalmic Limited, Dunedin, New Zealand) over a mean of 10 months' follow-up. Patients undergoing shunt implantation are likely to have a compromised endothelium before surgery as a result of a combination of the factors mentioned in the beginning of this article. Postoperative inflammation and tube-endothelial contact may compromise the corneal endothelium further and increase the risk of corneal failure [44]. In this long-term follow-up of 60 patients (60 eyes) who were implanted with an Ahmed glaucoma valve (AGV) (New World Medical, Inc.; Rancho Cucamonga, California, USA), corneal decompensation or corneal graft failure was the commonest adverse outcome. Studies of rabbit corneal buttons have reported that the degree of endothelial cell damage when compared with controls is directly related to the duration of contact [45]. Lim [46] compared the degree of endothelial damage caused by contact with three different materials: silicone, polymethylmethacrylate (PMMA) and phosphorycholine polymer-coated PMMA (PC-PMMA). The degree of damage was least with PC-PMMA, and the author concluded that PC-coated technology might be effective in reducing corneal failure rate in aqueous shunt implantation.

Studies on measuring CED preaqueous and postaqueous shunt implantation are limited. A recent report [47•] by the American Academy of Ophthalmology stated that the principal long-term problem with anterior chamber aqueous shunts is corneal endothelial failure and commented that too few high-quality studies have been published to assess complication rates with different aqueous drainage devices. The recent tube versus trabeculectomy (TVT) study reported that the overall incidence of postoperative complications was higher in trabeculectomy than with aqueous shunts, but corneal edema was higher in the shunt group (7%) compared with the trabeculectomy group (3%). Loss of vision occurred in eight patients (eight eyes) with persistent edema, and multivariate analysis revealed that corneal edema was an independent predictor for visual loss even after adjusting for unoperated cataracts [41••]. Stein *et al.* [48•] conducted a study that looked at postoperative adverse outcomes after glaucoma surgery amongst Medicare beneficiaries between 1994 and 2005; they found adverse outcomes to be higher after shunt implantation as compared with primary trabeculectomy and trabeculectomy with scarring. They speculated the reason for the higher complication rate was case selection rather than surgery or the implant itself. Kim *et al.* [49••] reported CED loss 1, 6 and 12 months after surgery in a consecutive series of 30 eyes that underwent AGV implantation. The mean CED loss was 3.5, 7.6 and 10.5% at 1, 6 and 12 months, respectively. The superotemporal area (closest to the tube) exhibited the greatest cell loss in comparison with central cornea. The authors concluded that great care should be exercised with AGV implantation to minimize endothelial loss. This study is one of the few prospective studies that measured CED loss in patients implanted with aqueous shunts, and their findings suggest that CED loss continues up to 1 year after AGV implantation. Further, longitudinal studies are required to clarify the long-term effect of shunts on the corneal endothelium

and, in particular, to evaluate the significance of shunt position in relation to the endothelium.

Corneal grafts

Corneal graft failure, secondary to shunt implantation, is a major concern in grafted eyes. A retrospective study [50] of 64 patients (78 eyes) with refractory glaucoma who underwent AGV implantation reported four eyes (5%) with failed corneal grafts that required repeat keratoplasty. Papadaki *et al.* [51•] evaluated 60 patients (60 eyes) with uveitic glaucoma who underwent AGV implantation over a 4-year period. Twelve eyes (20%) had a corneal graft before or concurrently with AGV implantation, of which five eyes (40%) had graft failure over a mean follow-up of 18 months. The authors concluded that corneal edema and graft failure were noted to be the most frequent complications in their study, and they suggested that patients with preexisting corneal disease or previous corneal graft should have the shunt inserted in the vitreous cavity to reduce the risk of corneal decompensation. Tello *et al.* [52•] recommended placing the shunt in the vitreous cavity to reduce corneal endothelial loss, especially in patients with compromised endothelium. Ritterband *et al.* [53••] performed a retrospective analysis of 83 eyes (80 patients) who underwent penetrating keratoplasty and primary placement or repositioning of a shunt through the pars plana from 1997 to 2005 and found that 59% (19/32) of corneal grafts remained clear at 2 years; they claimed that their rate of corneal graft failure was comparable to, or lower than, those reported in studies, in which shunts were placed in the anterior chamber.

Childhood glaucoma

Controlling IOP in congenital and childhood glaucoma is challenging. Previous studies have cited variable success with IOP reduction, with the use of aqueous shunts such as Baerveldt [54], primary trabeculotomy-trabeculectomy [55] and viscotrabeculotomy [56]. In those with corneal edema secondary to IOP elevation, IOP reduction can often reverse or reduce the degree of edema [55].

Epithelial downgrowth following goniotomy has been reported in one observational case report [57], in which an epithelial cyst appeared 1 year after goniotomy and previous Ahmed valve implantation. Although the cyst resolved after cryotherapy, the authors were not able to determine the origin of the epithelial downgrowth (the Ahmed valve or the goniotomy). Corneal decompensation has been reported as a complication of the use of shunts in the treatment of advanced childhood glaucoma [54]. Tube-corneal touch has been reported in 3–35% of children [58••], and patients younger than 2 years of age seem to be at higher risk (26%). O'Malley *et al.* [58••] assessed the use of aqueous shunts in refractory pediatric congenital and aphakic glaucomas and found that 5/10 required revision or repositioning because of tube-corneal touch, even though corneal decompensation was not observed, except in one case of corneal graft failure, despite the absence of tube-corneal touch. Tube-corneal touch might occur more commonly in neonates and children because the anterior chamber is smaller, or because of eye rubbing and changing tube position with growth of the eye [58••,59,60]. To reduce the risk, Tanimoto and Brandt [61] suggested inserting the tube so that it is positioned parallel to and as close to the iris as possible.

Transscleral cyclodiode laser photocoagulation

Transscleral laser cyclophotocoagulation (cyclodiode) is commonly used in the management of patients with recalcitrant glaucoma. However, single treatment failure is not uncommon, and further treatment is often required [62]. Corneal opacification has been reported in patients with corneal grafts; Shah *et al.* [63] reported that 3/19 (16%) eyes with originally clear grafts developed edema. More recently, Ocakoglu *et al.* [64] reported success with the use of cyclodiode in grafted patients, achieving an IOP less than 22 mmHg in 72% of eyes with or without medication at 1-year follow-up and no graft failure after treatment.

Conclusion

Corneal complications after glaucoma surgery continue to be a serious cause of surgical failure in patients with complex glaucoma. Improvement in surgical technique, especially with the judicial use of antiproliferatives and enhancing the biocompatibility of tube implants, may further reduce the risk of CED with filtration surgery. Recent results from the TVT study demonstrate comparable safety profile between trabeculectomy and aqueous shunts 1 year after implantation, but corneal complications still occurred more frequently after shunts. The relative influence of a number of risk factors is still unclear. These include proximity of the tube to corneal endothelium, implant material, surgical trauma and case selection, which are all potential reasons. Nonpenetrating surgery may have a lower complication rate than filtration surgery, but Descemet's membrane detachment can result in permanent reduction in vision. With NPGS gaining in popularity, further studies are required to determine whether long-term corneal complications occur in patients undergoing nonpenetrating surgery. Studies reporting CED in patients undergoing glaucoma surgery are rare; to clarify this relationship, further longitudinal study that involves assessing pre-CED and post-CED are required.

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