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Hypotony Keratopathy Following Trabeculectomy

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Precis: Hypotony keratopathy is a potential complication of hypotony following trabeculectomy and successful treatment depends on increasing intraocular pressure.

Abstract

Purpose: To evaluate corneal decompensation in patients following trabeculectomy with adjuvant mitomycin C (MMC). We propose “hypotony keratopathy” as a descriptive term.

Methods: Patients with trabeculectomy and follow up performed by the authors were included in this retrospective single center study. Patients were included if they had evidence of corneal decompensation (Descemet’s membrane folds [DMF] or corneal edema) following trabeculectomy with MMC with concurrent hypotony. Outcome measures included best corrected visual acuity (BCVA), average intraocular pressure (IOP) at time of diagnosis, and changes in central corneal thickness. Clinical outcomes to treatment of hypotony keratopathy were noted when performed.

Results: A total of 14 eyes from 12 patients were included in the series. Hypotony developed an average of 5 years after trabeculectomy, and hypotony keratopathy was diagnosed 7.5 years after trabeculectomy. Hypotony keratopathy ranged from non-visually significant DMF without increased corneal thickness to visually significant corneal edema. BCVA decreased zero to six Snellen lines after diagnosis of hypotony keratopathy. Lower IOP was associated with increased corneal thickness. Vision improved after trabeculectomy revision (six eyes) and cataract extraction with intraocular lens implant (CEIOL) (one eye) but did not improve after Descemet stripping automated endothelial keratoplasty (two eyes).

Conclusions: Hypotony keratopathy is a poorly described but potentially treatable complication of trabeculectomy with MMC. Hypotony keratopathy may be related to endothelial dysfunction secondary to hypotony.

Key words: glaucoma, hypotony, trabeculectomy, corneal edema

Introduction

Incisional glaucoma surgery is often performed in the course of glaucoma management but can be associated with sight-threatening complications. One cause of vision loss following glaucoma surgery is corneal decompensation.[1] Persistent corneal edema occurs more frequently following implantation of a glaucoma drainage device compared to trabeculectomy.[2] Intermittent tube to endothelium contact likely contributes a mechanical component to corneal decompensation following glaucoma drainage device implantation.[3] This may explain, in part, why penetrating keratoplasty grafts have lower rejection rates when the tube is placed further from the corneal endothelium.[4]

Persistent corneal edema is less common after trabeculectomy, occurring in only 3-5% of patients.[2,5] The causative factor for corneal edema following trabeculectomy is not well described or understood. Several case reports describe incidents of corneal edema following trabeculectomy with mitomycin C (MMC) and 5-fluorouracil (5-FU).[6–10] Corneal edema has also been described in rabbit models following trabeculectomy with MMC.[11] MMC and 5-FU are toxic to the endothelium at high doses but the typical concentrations used surgically are not detrimental to the endothelium in experimental models.[12–14] Further, almost 3% of patients had corneal edema following trabeculectomy even without the use of anti-metabolite.[5] This suggests other factors may lead to corneal edema following trabeculectomy.

Several case series describe corneal edema in patients with hypotony secondary to causes other than trabeculectomy.[15,16] Interestingly, another small case series of three patients with

chronic iridocyclitis and hypotony described transient corneal edema that improved following improvement of IOP.[17] One case of corneal edema following trabeculectomy also improved after IOP was increased by trabeculectomy revision.[10] However, the association between hypotony and corneal edema has not been well characterized. Here, we present a case series of 14 eyes with hypotony and corneal changes and propose "hypotony keratopathy" as a descriptive term.

Methods

This study is a retrospective single center case series. Clinical charts of patients seen in clinic were reviewed over 18 months (January, 2017 – June, 2018). Patients were included in the series if they had a history of trabeculectomy with MMC and subsequent hypotony (IOP < 8 mm Hg) accompanied by corneal changes. The corneal changes ranged from mild Descemet's membrane folds (DMF) with clear cornea to frank corneal edema. Only patients whose surgeries were performed by the authors and had available pre-operative baseline exams were considered eligible for inclusion. Patients with history of Fuch's endothelial dystrophy and hypotony maculopathy were excluded in an attempt to avoid secondary cause of corneal edema or decreased vision. A retrospective chart review of these patients was performed. The study was approved by the Institutional Review Board at the University of California, San Diego. The study was performed in accordance with the principles of the Declaration of Helsinki and HIPAA regulations.

Patient data including patient age at the time of trabeculectomy, time until hypotony and hypotony keratopathy was diagnosed, best corrected visual acuity (BCVA) post-trabeculectomy, BCVA post-hypotony keratopathy diagnosis, average intraocular pressure (IOP) in the three visits after hypotony keratopathy diagnosis, and central corneal thickness (CCT) prior to trabeculectomy and after hypotony keratopathy diagnosis were recorded. For patients that received treatment for hypotony keratopathy, type of treatment, BCVA following treatment, and IOP following treatment were recorded.

Results

The study comprised 14 eyes of 12 patients. Patient characteristics are listed in Table 1. The degree of corneal changes of patients included in the study ranged from mild non-visually significant DMF (Figure 1a) to visually significant corneal edema (Figure 1b). The average IOP in the three visits after the diagnosis of hypotony keratopathy ranged from 1 to 7.3 mm Hg, with an average of 4.2 mm Hg. Numerical hypotony (IOP < 8 mm Hg) developed an average of almost four years after trabeculectomy. Hypotony keratopathy was diagnosed an average of 7.5 years after trabeculectomy. BCVA following trabeculectomy was decreased zero to six Snellen lines at the time of hypotony keratopathy diagnosis. Patients were observed a further average of 1.5 years until they either had treatment for hypotony keratopathy or had their final clinic visit within the study period. Patients lost an average of one line during this period, although one patient improved by four lines.

Seven eyes had CCT measured following diagnosis of hypotony keratopathy (Table 1). Of those eyes, changes in corneal thickness ranged from -4 um to +176 um. Eyes with lower IOP tended to have a greater increase in CCT, although the association was weak (R^2=0.3126) (Figure 2). Two eyes had multiple measures of CCT. The CCT of one eye increased in thickness by 26 um (5.3%) at initial diagnosis of hypotony keratopathy and increased a further 30 um (5.8%) two years later. The other eye had a change of less than 10 um over a similar interval. The vision of the eye with increasing thickness lost one line, while the stable eye lost no lines.

Six eyes underwent surgery to correct visually significant hypotony keratopathy (Table 2). Three eyes underwent trabeculectomy revision. Of those eyes, one returned to baseline visual acuity, one improved to one line from baseline visual acuity, and one regained two lines (four lines from baseline visual acuity). Two eyes underwent Descemet stripping automated endothelial keratoplasty (DSAEK). One eye improved two lines (four lines from baseline vision); the other did not have improvement in visual acuity. One patient underwent cataract extraction with intraocular lens implantation. That patient improved to baseline visual acuity and the DMF resolved. Eight eyes were observed without intervention. Those eyes on average had no change in vision and IOP increased 3.2 mm Hg over the follow up period. One eye had an IOP increase of 9.3 mm Hg without intervention, and vision in that eye improved by four lines (to baseline BCVA).

Discussion

This case series of hypotony keratopathy illustrates the presence of a well-known, but poorly described, clinical entity. However, following the recent recall of a surgical device associated with endothelial cell loss, there is an increased interest in potential causes of corneal edema following glaucoma surgery.[18] There was a significant delay between initial surgery, development of hypotony, and development of hypotony keratopathy. Numerical hypotony and hypotony keratopathy did not develop until almost four years and 7.5 years, respectively, after trabeculectomy. The intraoperative use of MMC offers an early benefit of lower trabeculectomy failure rates but likely increases the risk of late complications such as hypotony keratopathy.[19] It was speculated that such complications could occur soon after MMC was introduced as an adjunct with trabeculectomy.[20,21] These potential complications were recently emphasized in light of the movement toward precision medicine.[22] The existence of hypotony keratopathy as a late complication lends further credence to the thoughtful and judicious use of MMC during trabeculectomy.

Hypotony keratopathy encompasses corneal changes ranging from mild DMF with clear cornea to extensive edema with bullous keratopathy. Interestingly, in two-thirds of patients DMF developed with less than a 5% change in central corneal thickness. DMF are frequently the first biomicroscopic sign of corneal edema, but when associated with edema do not become present until corneal thickness has increased by 20-30%.[23] DMF develop with corneal edema due to a decrease in posterior corneal curvature and subsequent deformation of the posterior corneal surface.[24] However, this study demonstrates that DMF can develop without significant changes

in corneal thickness. The DMF are thus likely related to structural changes of the eye itself, with decrease in posterior corneal curvature occurring due to factors other than corneal edema. The patients with DMF and stable corneal thickness maintained vision within one line of pre-operative BCVA, suggesting that DMF alone are not visually significant.

However, structural changes such as DMF can be accompanied by true corneal edema in hypotony keratopathy. Corneal thickness increased by more than 20% in one-third of patients that had CCT measured before and after the diagnosis of hypotony keratopathy. The development of true edema appears to be associated with lower IOP, although some patients with very low IOP had no increase in CCT. Hypotony keratopathy may exist on a spectrum, with some patients maintaining stable vision with only DMF for years, whereas other patients have functional decline and worsening vision as corneal edema develops. Worsening vision was associated with progressively increasing corneal thickness in the patients with serial CCT measurements. Thus, increasing corneal thickness may be an indication for surgical intervention in patients with hypotony keratopathy, whereas DMF alone with stable corneal thickness may be observed.

Corneal edema associated with hypotony keratopathy is frequently reversible when IOP increases. This suggests that the edema is due to endothelial dysfunction, not endothelial loss. Successful treatments for hypotony keratopathy include trabeculectomy revision and cataract extraction. Trabeculectomy revision successfully increased IOP and improved the vision in all three patients included in this case series. Cataract extraction also improved vision and led to

resolution of hypotony keratopathy in one patient included in this study. Cataract extraction was recently described as an effective treatment for hypotony.[25] Although the patient in this study only increased IOP by 1 mm Hg, this may have crossed the threshold for clinically significant hypotony and subsequently led to resolution of the DMF. DSAEK alone does not appear to be an effective treatment for hypotony keratopathy. The ineffectiveness of DSAEK is likely related to continued hypotony after the surgery, which may affect the functionality of the transplanted endothelial cells.

This study has limitations due to the retrospective nature of the study design. Moreover, the sample size is too small to address possible risk factors for development of hypotony keratopathy. Likewise, the incidence and prevalence of hypotony keratopathy cannot be estimated due to the potential loss to follow up of patients during the long delay between surgery and development of hypotony keratopathy. Patients with history of corneal dystrophy were excluded from the study, but specular microscopy was not performed so low corneal endothelial cell count prior to trabeculectomy cannot be excluded. Our definition of numerical hypotony is different from that of the World Glaucoma Association (IOP $\leq$ 5 mm Hg), but all patients meet the updated criteria (at least one visit with IOP < 7 mm Hg) proposed by Abbas *et al*.[26] Finally, the proportion of patients with low IOP that develop hypotony keratopathy was not examined. Despite these limitations, this case series offers new information regarding a poorly described and treatable clinical entity. Future studies may better elucidate the risk factors, physiology, and treatment of hypotony keratopathy.

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Table and figure captions:

Table 1: Characteristics of patients with hypotony keratopathy.

Table 2: Treatments and outcomes of hypotony keratopathy.

Figure 1: Slit lamp photos of hypotony keratopathy ranging from mild Descemet's membrane folds (Fig 1a) to visually significant corneal edema (Fig 1b).

Figure 2: Relationship between intraocular pressure and the number of lines lost after diagnosis of hypotony keratopathy.