CORNEAL COMPLICATIONS OF INTRAOPERATIVE MITOMYCIN C IN GLAUCOMA SURGERY

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ABSTRACT

Purpose: To report corneal toxicity of Mitomycin C application during filtering glaucoma surgery in two patients.
Case Reports: An elderly woman, 81 years of age, developed diffuse corneal epitheliopathy with subepithelial stromal oedema seven weeks after a trabeculectomy with Mitomycin C application.
Another patient, a 76 year old man, first developed a central epithelium defect and stromal oedema in the second postoperative week after a similar procedure. Later the corneal stroma melted, what resulted in perforation in the second postoperative month.
Results: Intraoperative Mitomycin C application during trabeculectomy induced serious corneal complications several weeks after the surgery.
Conclusions: Although infrequent, serious corneal complications may arise following the intraoperative use of Mitomycin C in filtering surgery for glaucoma. The possible contributing factors to the development of the corneal toxicity will be discussed.

KEYWORDS

Mitomycin C, corneal complications

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INTRODUCTION

Mitomycin C (MMC) is an alkylating antibiotic derived from *Streptomyces caespitous* with antineoplastic and antifibroblastic properties (1,2,3). The antifibroblastic activity of MMC has proven to be beneficial to modulate the wound healing after pterygium excision, refractive surgery and to reduce cicatrisation after trabeculectomy as primary surgery and in cases of complicated glaucoma (4). The concentrations of MMC used during trabeculectomy range from 0.1 mg/ml to 0.5 mg/ml (5). Reported complications following the use of MMC are infrequent but may be severe and even sight treathening, including necrotizing keratitis (6). The well known complications are a shallow anterior chamber, acute and chronic hypotony, hypotony associated maculopathy, choroidal detachment, scleral thinning, blebitis and bleb-related endophthalmitis (4,7). In this article we describe two cases of corneal complications after trabeculectomy in whom MMC was used. Toxicity of MMC on the endothelial cells, keratocytes and the limbal stem cells has been described (8,9,10,11). The toxic effects of MMC on cultured porcine keratocytes and endothelial cells has been proven to be dose-dependent and worse for the mitotic keratocytes (9). Endothelial cell DNA cross-linking, DNA damage, and endothelial cell death via apoptosis has been demonstrated in laboratory experiments after topical application of 0.02% MMC (12). A significant endothelial cell loss has been seen immediately after MMC-augmented trabeculectomy which may result in clinically observed early corneal edema or persistent corneal edema that may require penetrating keratoplasty (4,7,8,13,14).
Inferring from the paucity of reported clinical observations of MMC toxicity on the corneal epithelium, one may assume that the corneal epi-

thelium is more refractory to damage by MMC. We could find only a single case report of delayed corneal epithelial toxicity and its successful treatment with limbal stem cell transplantation (15). In a prospective study on seven eyes, limbal avascularity with marked dry eye symptoms and problems of epithelium regeneration were observed in three eyes (16). One eye in this study showed corneal thinning. Corneal melting has been described after the use of MMC during pterygium excision (10,11).

CASE REPORTS

Our first patient was a woman, 81 years of age, who underwent trabeculectomy on her left eye for primary open angle glaucoma. At the filtration site, three sponges soaked with MMC 0.2 mg/ml were applied for three minutes under the fornix based dissection flap of Tenon's capsule intraoperatively. Care was taken not to expose the edges of the conjunctival incision to the drug. A fourth MMC soaked sponge was placed under the sceral flap. All sponges were removed after 3 minutes and the space between the conjunctiva and sclera was thoroughly irrigated with balanced salt solution (BSS). On the first postoperative day, a horizontal corneal erosion was noticed in the operated eye. Seven weeks after surgery, a diffuse epithelopathy with subepithelial stromal oedema of the cornea developed (*Fig. 1,2*). She was treated with retinol palmitate eye ointment (Vitapos®) twice daily. Two weeks later, interlacing horizontal line of damaged corneal epithelium still stained with fluorescein. Three months after the initial surgery, some fluorescein positive punctate spots were still present. Her visual acuity had reverted to the preoperative level of 0.6.

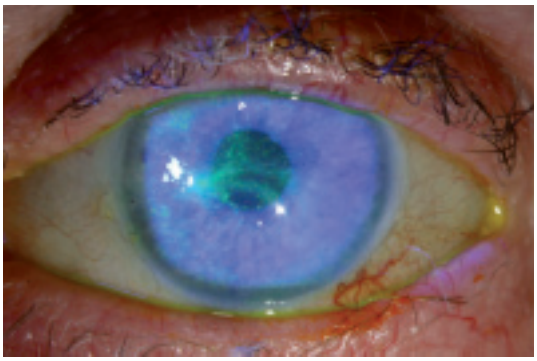

Fig. 2: Patient 1. A diffuse epitheliopathy with subepithelial stromal oedema, three weeks after trabeculectomy with MMC: horizontal fluorescein positive corneal erosion and puntactate keratitis.

Our second patient was a 76 years old man, who suffered from dry eye due to meibomian gland dysfunction and open angle glaucoma. A trabeculectomy was performed on his right eye with the same technique as used for the first patient. He presented with an epithelial defect on the central cornea two weeks later. During the ensuing two weeks, the central erosion enlarged to cover one third of the cornea accompanied by corneal swelling. The patient was hospitalized and treated with topical corticosteroids, retinol palmitate eye ointment, and one hourly rinsing of the eye with Hartmann solu-

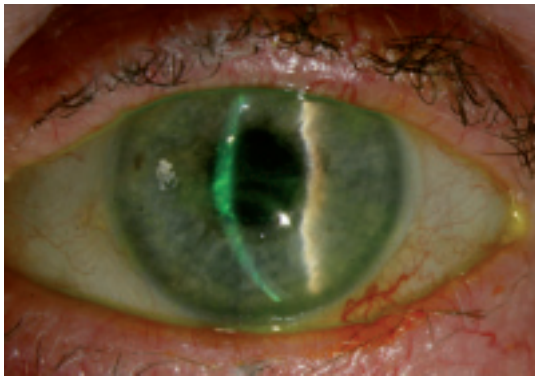

Fig. 1: Patient 1. Diffuse epitheliopathy with subepithelial stromal oedema, three weeks after trabeculectomy with MMC.

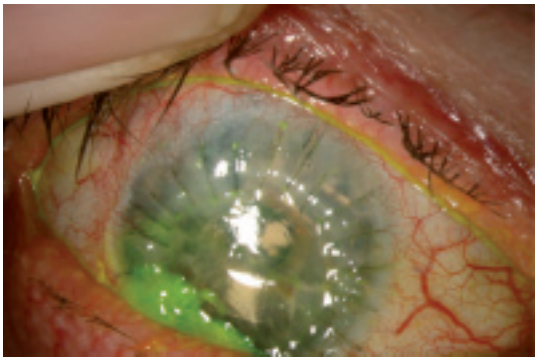

Fig. 3: Patient 2. Note corneal oedema of the host cornea and flattened donor button because of suture tension. Photograph taken after second keratoplasty due to corneal perforation.

tion. Nevertheless, the corneal stroma melted leading to corneal perforation during the second postoperative month. A penetrating keratoplasty was performed. In the following months two periods of hospitalization were necessary to treat new epithelium defects. Four months after the initial operation, a second corneal graft was required because of a new perforation. The host corneal rim was still edematous at the time of writing this report (*Fig. 3*). The visual acuity was reduced to detection of hand movements at two meters.

RESULTS

Two patients developed serious corneal complications several weeks after the intraoperative application of MMC during trabeculectomy. The first patient showed corneal surface epitheliopathy that appeared seven weeks after surgery in the first patient. It subsided under retinol palmitate ointment treatment. The second patient presented with a central epithelial defect in the second postoperative week which culminated in corneal melting and perforation in the second postoperative month.

DISCUSSION

The two glaucoma patients in this study demonstrate that serious corneal complications may arise following the intraoperative use of MMC in filtering surgery. The toxic effects of MMC on cultured porcine keratocytes and endothelial cells have been demonstrated in the past (9). However, the first symptoms in our two patients were caused by epithelial damage. One of these patients developed corneal perforation because of corneal melting. We could find only one published report of delayed corneal epithelial toxicity as a late complication of antimetabolite-augmented trabeculectomy which required limbal stem cell transplantation (15). Another case report described corneal thinning and wound dehiscence of a penetrating keratoplasty following trabeculectomy with intraoperative MMC application (6). In another interventional small case-series, three of the seven patients (43%) had marked dry eye symptoms and severe problems of corneal epithelium regeneration after trabeculectomy with MMC (16). In two of these patients, scleral melting occurred. In this interventional study, MMC was injected under the conjunctiva in a dosage of 0.2 mg/ml at the start of filtering surgery, and no irrigation with BSS as was employed.

Numerous reports exist about the corneal complications after the intraoperative use of MMC during phototherapeutic keratectomy and pterygium surgery. Kymionis et al described a dry eye problem after intraoperative topical MMC application during photorefractive keratectomy (17). The corneal epitheliopathy described by them was similar to the findings of our first case report. Similarly, corneoscleral melt with perforation has been reported after a single intraoperative application of MMC 0.02% on the scleral bed during pterygium excision, even though the sponges with MMC were removed after 3 minutes and the sclera was copiously irrigated with two 15 ml bottles of balanced salt solution (11). The melting had started after minor trauma to the eye. In another case corneoscleral perforation after MMC use during pterygium excision occurred spontaneously i.e. without trauma (10). In a series of 100 eyes undergoing pterygium surgery, 26% of the patients developed photophobia postoperatively which was attributed to superficial punctate keratitis (18). Four of these eyes (4%) developed progressive thinning of the bare sclera.

Contrary to the reports cited above, a number of retrospective case series have concluded that MMC was safe for the cornea. After application of MMC 0.2mg/ml for 2 minutes in 13 eyes during phototherapeutic keratectomy followed by vigorous rinsing of the eye with 30 ml balanced salt solution, no difference in healing time of the epithelial defect in the patients with or without MMC use was observed (19). Complications like corneal or scleral melting and endothelial toxicity was equally absent. Despite of such reports, patients with conditions predisposing to ulceration or poor wound healing should not be considered for MMC therapy. These group of patients include patients with Sjogren's syndrome, severe keratoconjunctivitis sicca, severe meibomian gland dysfunction, blepharitis, acne rosacea, atopic keratoconjunctivitis, uveitis, neurotrophic keratitis or herpes simplex keratitis (11).

Sodium hyaluronate eye drops prescription has been recommended as a preventive measure to curtail the ocular toxicity of MMC. In a prospective study on 68 eyes, the incidence of avascular blebs and bleb leakage was reduced by postoperative sodium hyaluronate eye drops instillation (20). The exact mechanism of the beneficial effect of sodium hyaluronate in such eyes is not known, although it has been suggested that the sodium hyalorunate eye drops may prevent the development of postoperative corneal epitheliopathy by washing out the remaining MMC from the ocular surface.

CONCLUSIONS

The development of MMC related corneal damage in two patients after trabeculectomy described by us in this paper re-emphasizes the reported potential corneal toxicity of MMC in the literature. In one of our patients the postoperative epithelial defect took 3 months to heal whereas the second patient required corneal grafting because of stromal melting and perforation. MMC is a powerful tool for wound modulation, whether it is applied to enhance the result of filtering surgery for glaucoma, to reduce corneal haze after refractive surgery or to prevent recurrence of pterygium. However, its alkylating and antifibrotic properties exert toxic effects on the corneal endothelial cells, keratocytes and the limbal stem cells. Therefore, MMC must be used cautiously in patients with ocular conditions predisposing to poor wound healing or ulceration.

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