

Mitomycin-C in Glaucoma Filtering Surgery

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Introduction

New concepts in glaucoma therapy have led to remarkable achievements in the 20th century. Recently-introduced drugs not only reduce intraocular pressure (IOP), but also aim to provide neuroprotection and increased retinal circulation. However, the practical approach remains the gold standard of glaucoma treatment, i.e. reduction of IOP by means of medication, laser surgery, or conventional surgery to obtain a safe target pressure. The surgical filtering procedure with adjunctive antimetabolites is still an excellent choice for reducing IOP in patients with advanced glaucoma.

A variety of antimetabolites, including mitomycin-C (MMC) and 5-fluorouracil (5-FU), are available for reducing IOP. Since MMC was first introduced for ophthalmologic use, and has been studied in-depth at the Department of Ophthalmology, at the National Taiwan University Hospital, this brief review will focus on MMC.

MMC was first developed in 1955 by Hata *et al.*, from *Streptomyces caespitosus*.¹ MMC inhibits cell mitosis by interrupting DNA synthesis, and probably also acts on the vascular endothelium. The late Kunitomo of the National Taiwan University first introduced this agent to

ophthalmology as a topical drop for prevention of recurrent pterygium.² In 1981, Chen, a former student of Kunitomo, was the first to use MMC intra-operatively for refractory glaucoma.³ This first patient had lost one eye in a traffic accident and had refractory high IOP in the remaining eye after cataract extraction, corneal transplant, and repeated filtering surgery (figure 1).

Adjunctive MMC application during filtering surgery has since been popularised for refractory glaucoma, and has been reported to maintain the filtering effect in patients with childhood glaucoma and secondary glaucoma, as well as when used in initial surgical approaches

for primary open angle glaucoma. However, such procedures are not without complications.

The first reported adverse effects of MMC were scleral changes, such as scleral melting in cases of pterygium excision. Complications may appear early, or as late as 15 to 20 years after MMC application (figure 2). MMC can also cause ocular complications and toxicity in glaucoma surgery. Eye surgeons must therefore exercise caution to avoid serious complications when performing MMC procedures.

Indications

In 1990, Chen *et al.* demonstrated that intra-operative MMC application is indicated for treatment of patients for whom filtering surgery carries a high risk of failure.⁴ Their study of MMC and fibroblast inhibition indicated that activated fibroblasts are one of the major factors leading to failed filtering surgery.

The indications for MMC set forth in their series included failure of previous filtering operations, previous intraocular

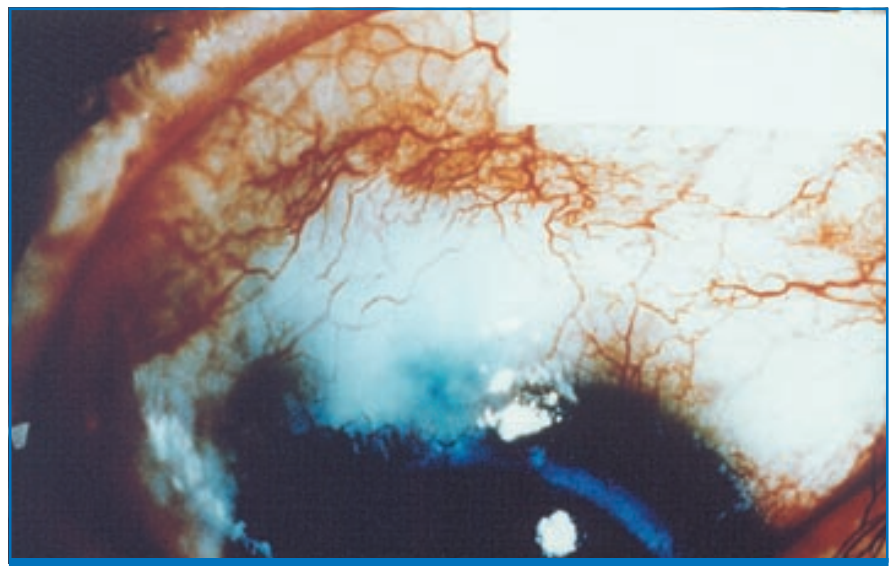
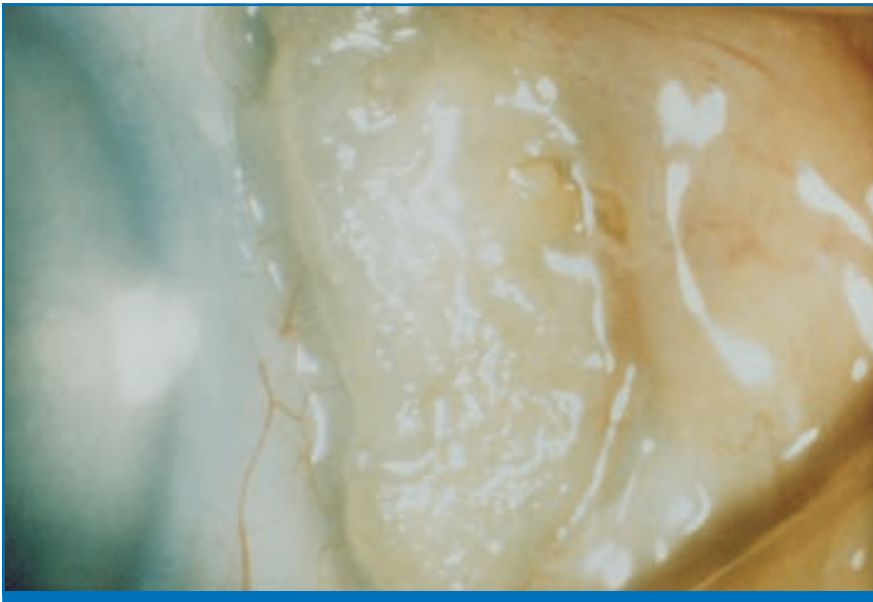


Figure 1. First application of adjunctive mitomycin-C in refractory glaucoma, 1981.³ Photograph reproduced courtesy of Professor Chen.

Figure 2. Necrotising scleritis after application of mitomycin-C eye drops for prevention of pterygium recurrence after excision.



surgery, high scar tendency related to race, and a strong inflammatory reaction in patients with secondary glaucoma.⁴ However, a recent study indicated that intra-operative application of MMC can increase the success rate of initial trabeculectomy for patients with primary glaucoma, even for younger age groups.⁵ The indications for adjunctive MMC application in filtering surgery may therefore expand to include treatment of childhood glaucoma.

Complications

Past studies of postoperative application of MMC eye drops in pterygium excision provide valuable insight into the potential complications of intraocular MMC use. In subtropical areas such as Taiwan, recurrent pterygium is so common that 0.04% MMC solution is usually applied 4 times daily after pterygium excision. Poor wound healing, scleral ulcer, and even perforations may occur as early complications of MMC therapy. Serious long-term complications, usually appearing more than 10

years later, in the original pterygium excision site include scleral melting and necrotising scleritis (figure 2). Such scleral complications prompted Rubinfeld *et al.* to suggest that MMC should not be used to prevent pterygium recurrence in patients with poor ocular healing, as in those with Sjögren's syndrome, herpetic keratitis, or keratoconjunctivitis sicca.⁶

With increasing experience of the application of intra-operative MMC during the past decade, the minor complications of punctuate corneal erosion, poor conjunctival wound healing or leakage, and elongation of postoperative wound reaction have become almost negligible.

The most serious complications of MMC application include ciliary body toxicity and long-term hypotony of less than 5 mm Hg, which may induce macular change. Our stereoscopic fluorescein angiography study in 1992 showed only 2 cases of maculopathy in 30 eyes 18 months after MMC surgery.⁷ Moreover, MMC-related maculopathy may be reversible. The reported frequency of hypotony

after MMC treatment ranges from 1.5 to 35%, while approximately 4 to 10% of patients develop hypotonous maculopathy following various forms of MMC application. Such hypotonous maculopathy is seen frequently in young and myopic patients. The treatments for hypotonous maculopathy include autoblood bleb injection, scleral patching, and cryotherapy.⁸ However, the best approach is to prevent hypotony by regulation of the concentration and duration of MMC application, which can be accomplished with the use of releasable sutures or other methods (described below).

Dose and Duration of Mitomycin-C Application

Chen *et al.* originally reported that application of MMC at a concentration of 0.2 to 0.4 mg/ml for 5 minutes is adequate, and poses little risk of severe complications such as hypotony.⁴ However, Chen *et al.* also suggested that 0.2 mg/ml for 5 minutes may be the safest effective dose. In North America, an initial report indicated that application of 0.5 mg/ml MMC for 5 minutes could result in severe hypotony associated with maculopathy. In our department, the dose of MMC for intra-operative application ranges from 0.2 to 0.3 mg/ml with durations ranging from 2 to 5 minutes according to the risk factors for bleb closure; these risk factors include patient age, previous operation, duration of antiglaucoma drug medication, and a tendency for wound scarring.

It is encouraging that a lower concentration of 0.02% twice daily has been recommended for prevention of recurrent pterygium.⁹ In addition, some institutes have shortened the duration of MMC application to 2 minutes when used for adjunctive trabeculectomy.¹⁰

Because of the high prevalence of primary angle closure glaucoma in Asia, trabeculectomy with releasable sutures is probably safe for treatment of shallow anterior chamber glaucoma, with the goal of early restoration of the anterior chamber. Therefore, the concentration and duration of MMC application are also important in trabeculectomy for primary angle closure glaucoma. MMC application can also yield effective bleb formation after restoration of the chamber followed by releasing suture and digital pressure.

Subconjunctival Injection

With intra-operative application and washing techniques, the amount of MMC left in the eye is quite variable; it may also vary considerably among surgeons. Because of the potential adverse effects of MMC in pterygium surgery, as well as the possible cytotoxicity of MMC in the ciliary body, a variety of approaches have been tried to precisely control the MMC dose. Although drug carriers and controlled delivery implants have been used in an attempt to control the MMC dose more precisely, simple subconjunctival injection appears to be most practical and least invasive method.^{11,12}

In 1992, we first reported the use of simultaneous sclerostomy and subconjunctival MMC injection.¹¹ The sclerostomy was performed with a THC: YAG laser probe subconjunctivally in rabbits, and IOP and bleb survival were monitored. This procedure proved to be effective in enhancing bleb filtration. A similar rabbit experiment was reported in 1994 by Karp *et al.*¹³

Using the results of these animal studies as a starting point, we investigated the use of MMC subconjunctival

Figure 3. Subconjunctival mitomycin-C solution injection 24 hours prior to trabeculectomy.



injection prior to trabeculectomy in patients with refractory glaucoma in 1995.¹⁴ The total dose of MMC injection was 1 to 3 μg (0.05 ml of a 0.02 mg/ml solution), 24 hours to 5 days prior to filtering surgery. The 27-gauge needle was inserted more than 1 cm away from the limbus to reach the planned trabeculectomy site, and the subconjunctival MMC solution was spread using the same needle (figure 3). During the follow-up period of more than 12 months, we observed significant IOP control and typical MMC blebs with diffuse, non-vascular appearance. Complications were minor.

The most important consideration in pre-operative subconjunctival MMC injection for filtering surgery is optimization of the MMC dose. Ando *et al.* showed that when 0.2 mg/ml MMC is injected subconjunctivally, followed by thorough washing 5 minutes later, approximately 3 μg of MMC remains in the eye.¹⁵

Subconjunctival administration of MMC prior to filtering surgery appears to be a safe and easy procedure. Its advantages include exact control of the amount of MMC delivered, prevention

of back-flow of MMC intracamerally via a fistula during intra-operative use, and the fact that it improves the ease of the fornix-based conjunctival flap procedure. However, the procedure can be difficult in patients with a very thin conjunctiva or thick conjunctival scarring, and MMC can be difficult to place in the infrascleral lamella.

Conclusion

This brief review has described the background of intraoperative MMC application in ophthalmic procedures, as well as its indications and possible complications. Because of the potential complications, the concentration and duration of MMC application must be carefully controlled; a new approach, pre-operative subconjunctival injection, appears to have great advantage in this regard. The development of MMC and other antimetabolites has started a new era for glaucoma filtering surgery.¹⁶ However, the risk-benefit ratio for the patient should be carefully weighed prior to surgery using MMC or similar agents.

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