5.1. Intraoperative use and needling bleb revision with mitomycin C

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Introduction

Mitomycin C (MMC) is an antibiotic derived from *Streptomyces caespitosus.* It is an alkylating agent which cross-links DNA, inhibiting the synthesis of protein and DNA, as well as inhibiting mitosis. It acts at all stages of the cell replication cycle, inhibiting both dividing and resting cells.

Mechanism of action

MMC when applied topically or injected subconjunctivally, prevents proliferation of fibroblasts within the subconjunctival space and tenon's capsule. It also has a lethal effect on vascular endothelial cells. *A single application of MMC can cause localized, irreversible inhibition of both fibroblasts and vascular endothelial cells. MMC is estimated to be 100 times more potent than 5-FU in fibroblast inhibition*[1].

Another proposed mechanism for lowering the intraocular pressure (IOP) with MMC application is the direct cytotoxic effect on the ciliary body[2]. The ocular structures are highly permeable to MMC, unlike 5-FU. MMC permeates through the sclera into the ciliary body. Subconjunctival injection of MMC, 0.5 ml of 0.2 mg/ml led to mean IOP decrease of 6 mmHg two months in blind glaucomatous eyes in a prospective study[3].

MMC is stable in buffered solutions and can be stored at 4 °C for extended periods of time (months to years) with little loss of efficacy[4]. There are, however, concerns regarding the sterility of the solutions and the consensus is that they should not be used more than a week after reconstitution.

Intraoperative use of mitomycin C with trabeculectomy and deep sclerectomy

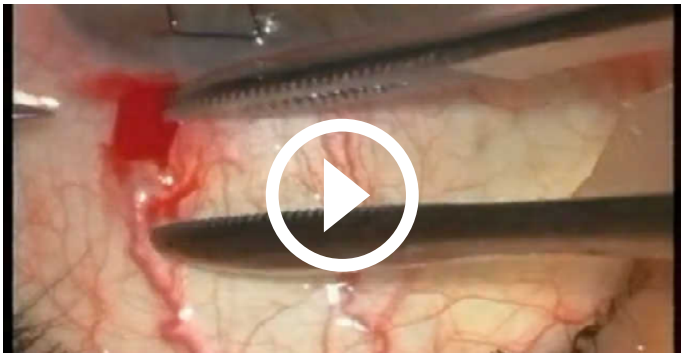
MMC is used to enhance the IOP lowering effect of trabeculectomy, bleb-dependent non-penetrating glaucoma procedures such as deep sclerectomy (DS) and with tube procedures. There is significant variation in dose, duration and technique of MMC application.

A survey of ophthalmologists showed that MMC application times vary between 5 seconds and 7 minutes, and concentrations between 0.1 mg/ml and 0.8 mg/ml. The literature does not give clear guidance as to the effective concentration and duration of application of MMC during trabeculectomy. It would appear that the higher dosing regimens used in earlier reports may have been excessive and similar outcomes may be achieved with lower dosing schedules[5,6]. Higher concentrations lead to a significant incidence of hypotony[7].

Intraoperative MMC in concentrations of 0.1-0.3 mg/ml applied for 1-3 minutes is adequate for all except very high-risk eyes

MMC application technique can be altered to reduce complications[8]. The technique for MMC application for trabeculectomy and DS is similar. The video (Video 1) shows the technique and is as follows:

- A fornix-based conjunctival flap may be preferable to the limbal-based approach. It is easier to perform and allows posterior dissection. Contact with the cut end of conjunctival flap can be avoided by means of a Khaw's conjunctival clamp (Duckworth-Kent™, UK) and may help prevent early leaks and late anterior cystic blebs (Figure 1).
- MMC may be applied before or after sclera flap dissection (superficial flap in case of DS).
- MMC-soaked sponges should be placed under the Tenon's capsule about 6 mm posterior to the limbus and over a wide area, at least one quadrant. This diffuse posterior application may help avoid the typical anterior cystic blebs associated with MMC use.
- Polyvinylalcohol (PVA) sponges are preferable to cellulose sponges as the latter may fragment and may be left behind.
- In trabeculectomy, the lateral edges of the sclera flap should not be extended into cornea. Early hypotony can be avoided by watertight closure of the scleral flap in trabeculectomy.



Video 1. Technique for conjunctival flap dissection and mitomycin C application.

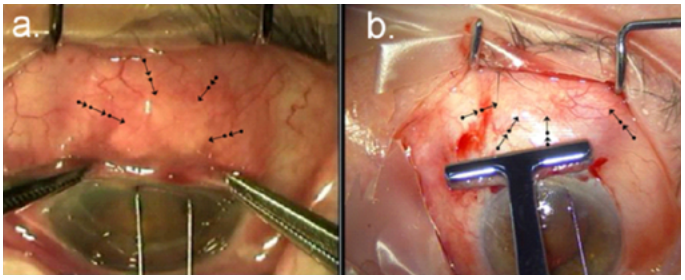


Figure 1. A. MMC applied anteriorly over scleral flap. This technique results in a high incidence of avascular blebs and leaks in the long-term. **B.** MMC application to a wider and more posterior part of the sclera, resulting in diffuse blebs with normal vascularity.

The MMC filtering bleb morphology

The optimum conjunctival filtration bleb after antimetabolite-enhanced trabeculectomy should be diffuse, extending posteriorly, hypovascular but devoid of cystic areas (Figure 2).

Leaks are usually observed in blebs with large avascular areas and increase in frequency with time in these blebs (Figure 3).

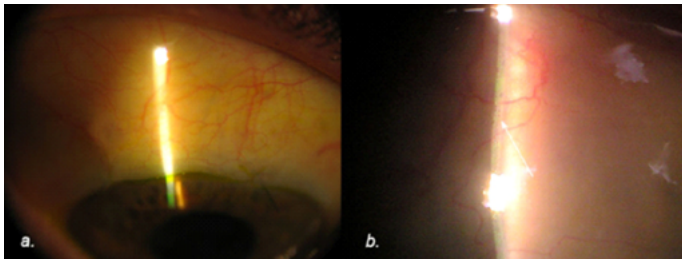


Figure 2. A. Ideal MMC bleb. **B.** Subepithelial microcysts.

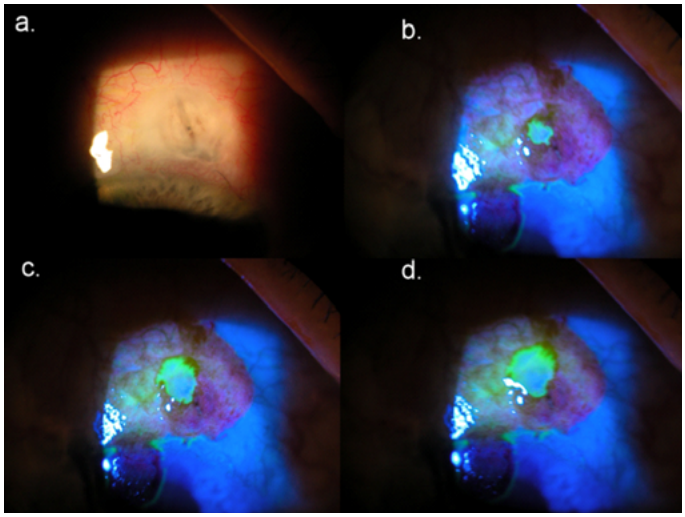


Figure 3. Bleb leak observed 2 years after DS with anterior MMC application. IOP was 12 mmHg. These leaks are only observed on application of concentrated fluorescein dye and increase the risk of bleb infections and endophthalmitis.

Mitomycin C will amplify and prolong complications due to poor surgical technique. These include prolonged conjunctival edge leaks, shallow anterior chamber, choroidal detachments and hypotony.

The majority of complications after filtering surgery are related to the conjunctival filtering bleb morphology. The 1990s saw an increased use of both 5-FU and then MMC during trabeculectomy. This has been associated with an increase in observed thin walled, avascular, cystic blebs which were prone to leakage. This lead to a very high incidence of bleb infections and delayed hypotony after trabeculectomy[5,6].

In a prospective study, a very high incidence of bleb avascularity, transconjunctival oozing and delayed leaks were observed after trabeculectomy and deep sclerectomy with *anterior* MMC application. Bleb avascularity was observed in about 70% of eyes 2 years after surgery and tended to precede transconjunctival oozing by 3 months. By Kaplan-Meier analysis the probability of observing bleb leaks increased from 1% at 6 months to 26% at 2 years[8].

The risk of thin avascular blebs after MMC-enhanced surgery can be decreased by the technique of broad posterior MMC application described above[9,10] .

Needle revision with MMC

The most common cause for failure after initially successful trabeculectomy is fibrosis in the subconjunctival tissues. Less commonly it may be due to sub-scleral fibrosis. Needle revision (NR) with injections of 5-FU or MMC can be done to re-establish aqueous outflow into the subconjunctival bleb. 5-FU is the most frequently used antifibrotic but MMC use is being reported more frequently in the recent years.

NR success depends more on individual characteristics of the patient and the type of bleb rather than the antifibrotic alone. It is more likely to fail in eyes with aggressive healing such as those with uveitis and patients of African ancestry. Gonioscopy is essential to ensure patency of the fistula (Figure 4). If the internal opening (sclerostomy) is blocked NR is unlikely to succeed (Figure 5). NR in eyes with scleral flap fibrosis is unlikely to succeed on first attempt and failure to detect a subscleral cleft is a poor prognostic indicator (Figure 6). Repeated NR in these cases may lacerate the sclera and create a full-thickness fistula.

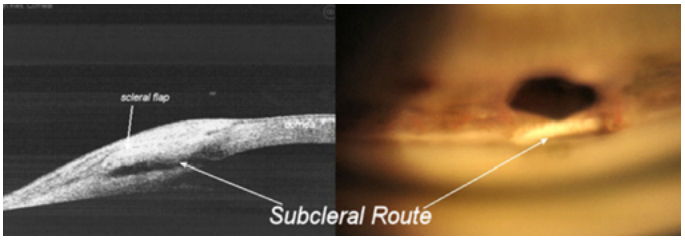


Figure 4. Anterior segment OCT and goniophotography showing the subscleral route (cleft) for aqueous drainage.

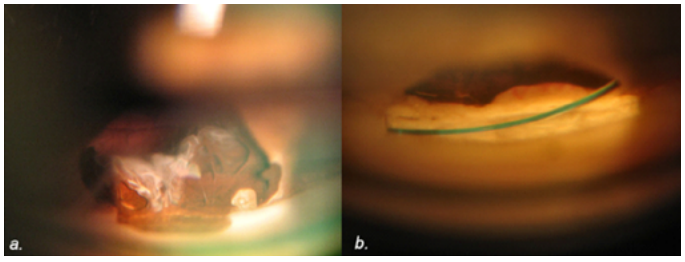


Figure 5. Gonioscopy in 2 eyes with ECCE and trabeculectomy. A. Vitreous and uveal tissue are blocking the sclerostomy. B. The IOL haptic is in the fibrosed internal sclerostomy.

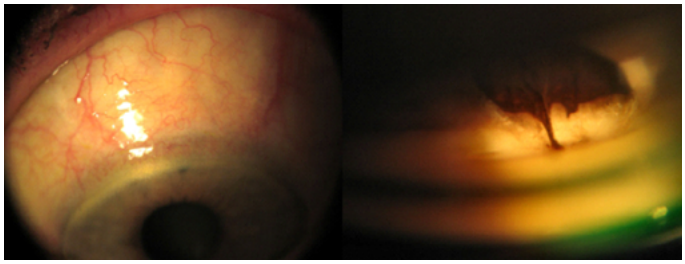


Figure 6. A flat bleb with subscleral fibrosis, This is manifested internally by the absence of the subscleral cleft. In this case vitreous and uvea are also blocking the internal sclerostomy.

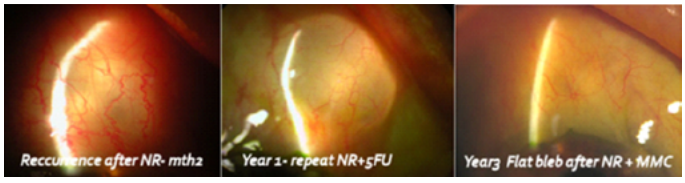


Figure 7. Recurrence of encapsulation after needle revision and eventual failure of bleb.

NR of encapsulated blebs is controversial with varying degrees of success reported by different authors. One randomized controlled trial showed no difference in IOP compared to the use of medications[11]. There is a high frequency of recurrence of encapsulation (Figure 7).

NR in the early postoperative period is more accurately called *needle flap elevation.* 5-FU is preferable to MMC in these cases especially if MMC has been used intraoperatively.

Technique for needle revision with MMC

The technique for needle revision (Figure 8) is shown in the videos (Video 2a and Video 2b). Performing it under the operating microscope rather than the slit-lamp bio-microscope (Video 3) affords better control and more chances of success. The tips for successful NR are as follows:

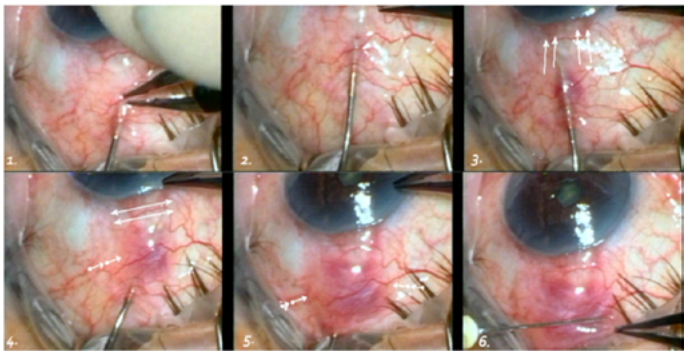
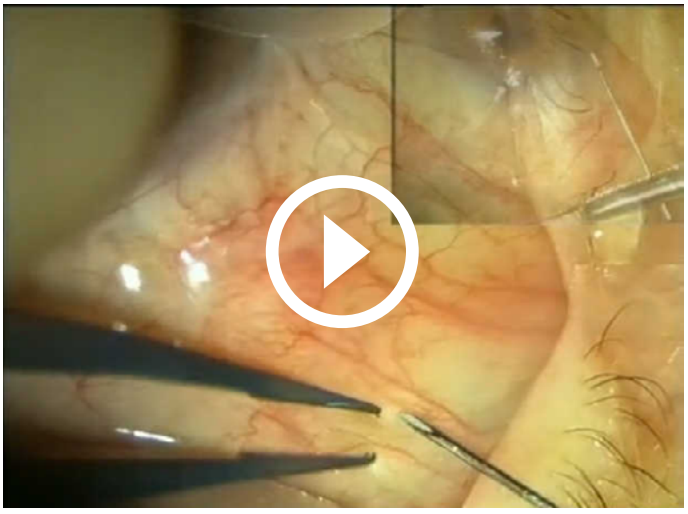
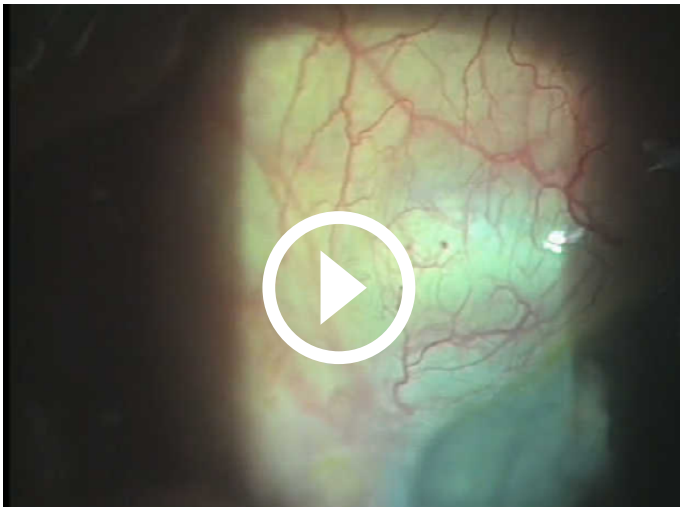


Figure 8. The technique for needle revision.



Video 2A. Needle revision for trabeculectomy and deep sclerectomy.



Video 3. Needle revision on the slit-lamp bimicroscope.

Video 2B. Needle revision after failed viscocanalostomy.

- Larger the gauge of needle used, more the complications. A 25-gauge needle is adequate for most procedures.
- Asses conjunctival mobility.
- Enter superior conjunctiva at least 10 mm from limbus and make a tract subconjunctivally to the region of fibrosis (long needle track).
- Initially stabbing, 'to and fro' motion of needle with multiple passes.
- Join these by moving needle sideways, using the bevel to cut.
- If excessive subconjunctival bleeding, *abandon procedure.*
- Always know where the needle is in subconjunctival/subscleral space.

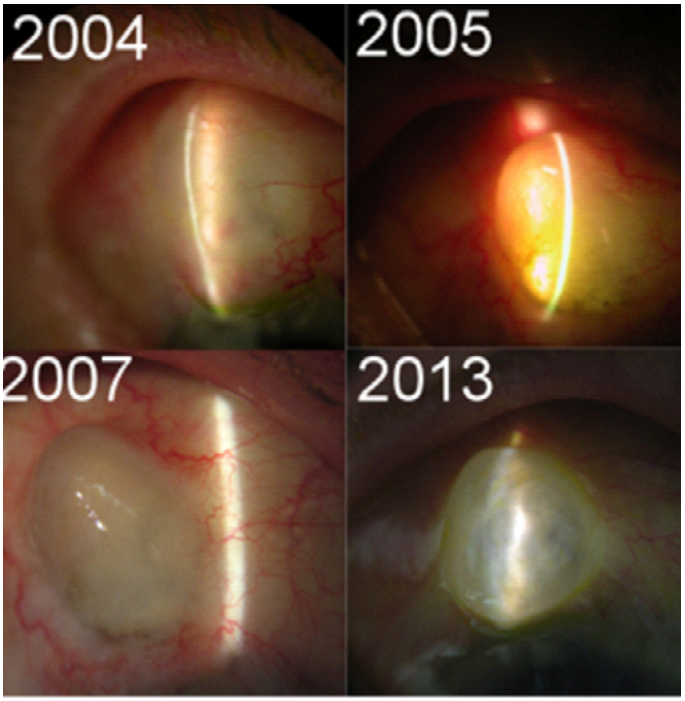
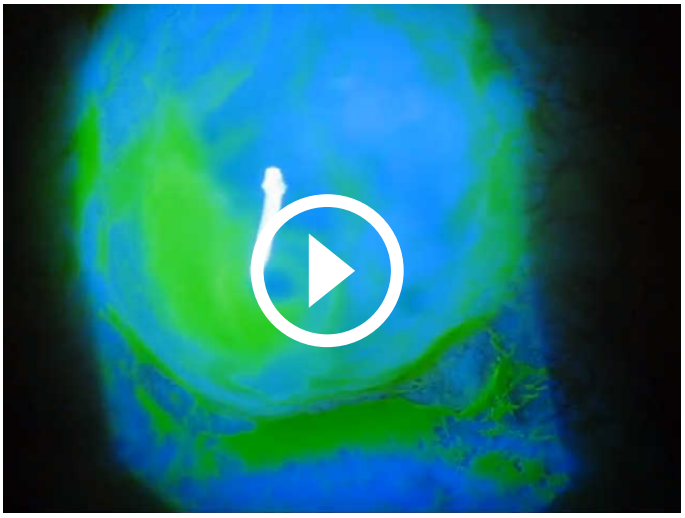


Figure 9. Eye with DS and MMC had 2 needle revisions with subconjunctival MMC 0.02 mg. Bleb leak and blebitis developed 9 years after the last NR procedure. The avascular bleb was excised and a Tutoplast™ patch graft was placed over the scleral flap (see Video 4).



Video 4. Repair of leaking bleb after Needle revision with MMC with Tutoplast Patch Graft.

- Entry into AC rarely needed.
- If blood tracks into anterior chamber:
  - Ask patient to shut eyes tight if on slit lamp.
  - AC washout, partial viscoelastic fill in OT.

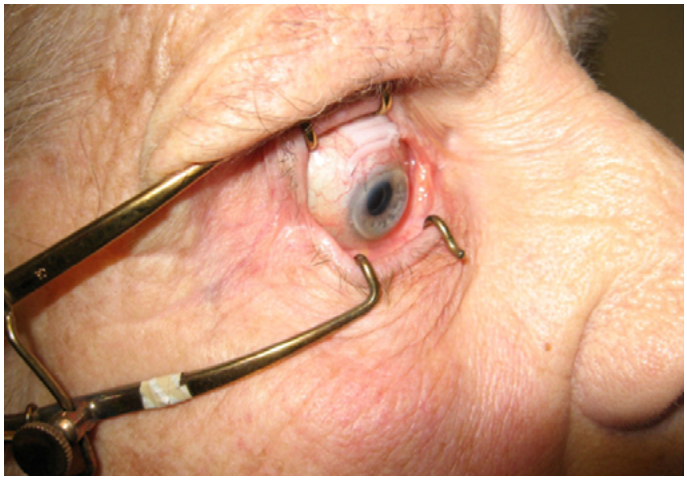


Figure 10. MMC application on conjunctiva. MMC 0.2 mg/ml for 3-5 minutes. Decrease duration to 3 minutes if eye has had previous exposure to MMC.

- Cautery to site of needle entry is optional.
- Take your time, it can take 5-10 minutes in difficult cases.

It is important to inject it 10-15 minutes *before* NR, to prevent it from entering the eye. Injection after the procedure is not advisable. The IOP is low and there negative pressure in the eye which can allow MMC to leak into the anterior chamber.

The dose of subconjunctival MMC is not clearly established and both low-dose (0.004 mg)[12] and high dose (0.04 mg)[13], have been reported. A dose of MMC 0.008 mg has been shown to be safe with no effect on corneal endothelial cell count and morphology. However success was associated with multiple procedures[14]. It is very important to keep in mind that the effect of MMC on the conjunctiva is permanent and cumulative. In some eyes, repeated injections of MMC may result in large avascular blebs and leaks (Figure 9). Transconjunctival MMC application (0.5 mg/ml for 6 minutes) is an alternative to subconjunctival injections has been described[15]. MMC diffuses into subconjunctival space at therapeutic concentrations (Figure 10).

Management after needle revision

Treat eye as after trabeculectomy with intensive topical and SC steroids. Supplementary 5-FU injections may be given depending on bleb appearance but subconjunctival MMC should be avoided. Avoid performing needle revision at close intervals and wait for the conjunctival inflammation to settle

Author	No	MMC dose	Mean interval from index surgery in months (SD)	Mean follow-up in months (SD)	Mean pre-needling IOP (SD)	Success criteria and rates
Mardelli *et al.*, *Ophthal* 1996	63	0.005 mg	>3	9.9 (3.7)	24.1 (6.4)	82.3% <15 mmHg at last FU
Shetty *et al.*, *J Glaucoma* 2005	44	0.04 mg	NS	>12 months	28 (8.2)	64% bet 4-22 mmHg at 1 year
Gutierrez-Ortiz *et al.*, *J Glaucoma* 2006	34	0.002 mg	4.4 (9.8)	14.2 (9.8)	25.5 (4.4)	41% <21 mmHg at last FU
Maestrini *et al.*, *Ophthal* 2011	125	0.008 mg (+ postop 5-FU)	5.3 yrs 2 (6 mths-30 yrs)	0.8 (12)	20.1 (5.2)	66% <16 mmHg at 3 years with/without meds

Table 1. Needle revision with MMC for trabeculectomy – published reports.

before performing the next NR procedure. This may mean waiting for 4-6 weeks.

Outcomes of MMC needle revision

Success of needle revision is variable and depends on type of bleb, length of follow-up and perhaps type of antifibrotic used. MMC is more effective than 5-FU for needle revision of failed trabeculectomy blebs[16]. Outcomes of some studies on NR with MMC are summarised in Table 1.

There is only one study on NR with MMC after DS. An IOP ≤18 mmHg or a 20% decrease from baseline with no glaucoma medications or further surgical procedures to lower IOP was achieved in 57% of eyes in 3 years and in 40% at 5 years. NR done with 6 months of DS were more likely to fail[17].

Complications

All NR procedures carry a higher risk of complications than trabeculectomy, as there is a rapid uncontrolled decompression of the eye. The most serious immediate complication is delayed suprachoroidal hemorrhage. Corneal epithelial stem cell deficiency (Figure 11) and endothelial decompensation may also occur (Figure 12).

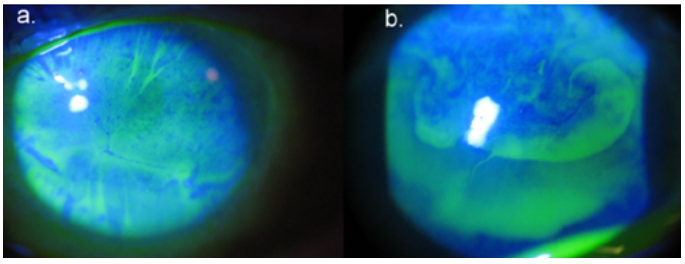


Figure 11. Two eyes with corneal epithelial stem cell deficiency after multiple exposures to MMC.

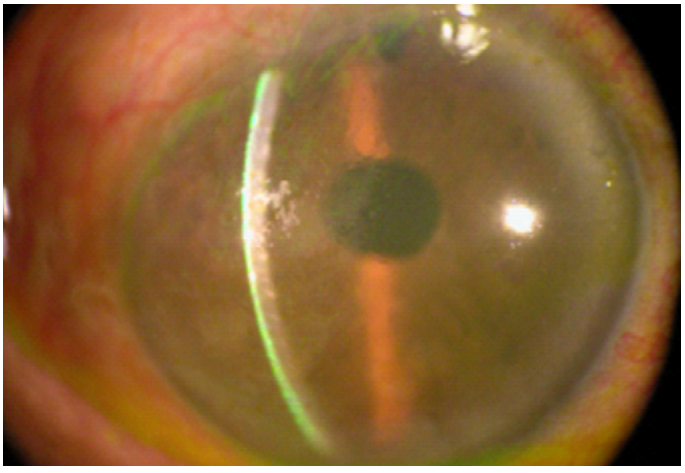


Figure 12. Eye with herpes simplex keratitis, DS with MMC and a previous failed trabeculectomy. Corneal endothelial decomposition started after NR revision with MMC, adjacent to the superotemporal bleb.

Figure 13. Successful NR with MMC 0.02 mg in 2004. Note a gradual disappearance of conjunctival vessels and by 6 years a large avascular cystic bleb had formed. Macular folds were observed. Bleb repair was done and the avascular areas were excised. The devitalized trabeculectomy site was reinforced with Tutoplast© and covered by a free conjunctival autograft from the inferior fornix.

Infections and hypotony, years after the procedure are important complications as mentioned previously (Figure 9 and Figure 13). Therefore repeated injections of subconjunctival MMC should be avoided.

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