REVIEW ARTICLE

Drugs 2006; 66 (3): 321-340
0012-6667/06/0003-0321/$44.95/0

Mitomycin
Clinical Applications in Ophthalmic Practice

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Abstract

Mitomycin (mitomycin C; MMC) is an antibiotic isolated from *Streptomyces caespitosus*. The drug is a bioreductive alkylating agent that undergoes metabolic reductive activation, and has various oxygen tension-dependent cytotoxic effects on cells, including the cross-linking of DNA. It is widely used systemically for the treatment of malignancies, and has gained popularity as topical adjunctive therapy in ocular and adnexal surgery over the past 2 decades.

In ophthalmic medicine, it is principally used to inhibit the wound healing response and reduce scarring of surgically fashioned ostia. Hence, it has been used as adjunctive therapy in various ocular surgeries, such as glaucoma filtering surgeries, dacryocystorhinostomy, corneal refractive surgery and surgeries for

ocular cicatrisation. In addition, it has been used as an adjunct in the surgical management of pterygia, ocular surface squamous neoplasia, primary acquired melanosis with atypia and conjunctival melanoma. In many of these surgeries and ophthalmic pathologies, MMC showed a significant beneficial effect.

Mitomycin (mitomycin C; MMC) has gained popularity as topical adjunctive therapy in ocular diseases over the past 2 decades. It is used as adjunctive treatment in various ocular surgeries. In addition, topical MMC is currently used in the treatment of ocular neoplasia. This article reviews the various applications of MMC in ophthalmic practice and the possible complications, with special emphasis on usage in various ocular surgeries and ocular surface neoplasia.

We reviewed the relevant medical literature by searching MEDLINE (1970–2005), using the keyword 'mitomycin C', and the combinations with the following keywords: 'eye', 'glaucoma', 'trabeculectomy', 'filtering surgery', 'filtering bleb', 'pterygium', 'dacryocystorhinostomy', 'lacrimal', 'myopia', 'cornea', 'conjunctival cicatrisation', 'ocular surface neoplasia', 'primary acquired melanosis', 'conjunctival melanoma' and 'complications'. Our search was mainly on human studies, as well as experimental models in animals, and preference was given to manuscripts published in English language journals. Articles from peer-reviewed journals were included for review. From these studies and their references, 986 abstracts were reviewed, and those pertinent to our discussion were selected. Major ophthalmic and medical textbooks were also reviewed for content, as well as original references, and these were manually searched. Clinical studies were selected if they were randomised controlled trials, single- or double-blind, or interventions where MMC was compared with placebo or other antifibrotic agents. Case series and single case reports were also included when reviewing experimental treatments. The commonly used terms used in this review are defined in table I.

1. Pharmacology and Pharmacokinetics

1.1 Structure and Mechanism of Action

MMC is an antibiotic isolated from *Streptomyces caespitosus*. It has a molecular weight of 334 daltons, and is soluble in water and organic solvents.[1] It contains quinone, carbamate and aziridine groups, all of which may contribute to its activity.

MMC is usually classified as an alkylating agent. All of the alkylating agents are electrophilic through the formation of carbonium ion intermediates. This results in the formation of covalent linkages to nucleophiles, especially with DNA, by alkylation of various moieties. MMC requires chemical or enzymatic reduction to bind DNA by mono or bifunctional alkylation.[2] Under anaerobic conditions, reduced MMC intermediates cross-link double stranded DNA. Although DNA alkylation can occur at any stage in the cell cycle, the biological consequences are most severe during DNA synthesis. In addition, inhibition of RNA and protein synthesis is a non-specific mechanism of cell toxicity.[3] Furthermore, under aerobic conditions, as occurs predominantly in ophthalmic use, intermediates react with molecular oxygen to generate free radicals, causing cytotoxicity via lipid peroxidation, and DNA and protein damage.[1]

In ophthalmic use, MMC has also been shown to inhibit cell migration and extra cellular matrix production.[4] An important mechanism of action in subconjunctival ophthalmic use, is the induction of apoptosis in Tenon's capsule fibroblasts.[5] The induction of apoptosis is thought to relate to the DNA damage either by alkylation or free radical injury.[5] Hence, there are a number of mechanisms by which MMC is toxic to both proliferating and non-proliferating cells. However, it is well known clinically that chronic tissue effects (to the conjunctiva) can occur for many years after a single topical application.[6,7] The exact mechanism of action of these chronic effects remains unclear.

Table I. Commonly used ophthalmologic terms and their definition

Trabeculectomy	Surgery for glaucoma that creates a fistula to facilitate drainage of aqueous humor from the anterior chamber to a subconjunctival space
Filtering bleb	The elevated area on the conjunctiva where the aqueous drains into after trabeculectomy
Overfiltration	Increased drainage of aqueous into the subconjunctival space as a result of reduced scarring
Hypotony	Very low intraocular pressure which causes structural changes in the eye as a result of overfiltration or leakage
Hypotonic maculopathy	Structural changes at the macula secondary to a very low intraocular pressure
Choroidal effusion	Collection of fluid in the suprachoroidal space
Hyphema	Blood in the anterior chamber
Intumescent cataract	Mature cataract that is swollen because of increased fluid within the lens
Scleromalacia	Severe thinning causing melting of the sclera
Endophthalmitis	Infection of ocular contents
Pterygium	A wing-shaped conjunctival overgrowth onto the cornea
Dacryocystorhinostomy	Surgery for blockage of the lacrimal drainage system where a passage is created between the lacrimal sac and the nose
Laser *in-situ* keratomileusis	Refractive surgery where laser is used to ablate and reshape the cornea after creating a corneal flap
Photorefractive keratectomy	Refractive surgery where excimer laser is used to reshape the cornea without creating a corneal flap
Cicatrisation	Excessive scar formation
Blepharospasm	Spasm of the orbicularis muscle causing very frequent blinking
Benign intracranial hypertension	Raised intracranial pressure with no evidence any pathology in the brain or meninges
Corneal ectasia	Thinning of the cornea
Punctate keratopathy	Small, multiple epithelial erosions on the cornea

1.2 Ocular Pharmacokinetics

Ocular pharmacokinetic studies in rabbits, using a subconjunctival injection of MMC, found a half-life of 0.18–0.30 hours for conjunctiva and 0.20–0.45 hours for sclera, and also that within 2–3 hours, the ocular tissue levels of MMC were minimal.[8] Seah et al.[9] found that MMC is detectable in the aqueous humor within minutes of external application in trabeculectomy. The aqueous humor concentration is greater with scleral application than with episcleral application. Irrigating the ocular surface with saline after application of MMC reduces the initial drug concentration to one-fifth in the sclera and to one-fifteenth in the conjunctiva; however, this does not change the half-life of the drug.[8]

2. Ophthalmic Applications

2.1 Ocular Surgery

MMC is now used as an anti-scarring agent in a wide range of ocular surgeries and laser assisted procedures; including glaucoma filtering surgery, pterygium surgery, lacrimal surgery, corneal refractive procedures and surgery for ocular cicatrisation.

2.1.1 Glaucoma Filtering Surgery

The conjunctival wound healing response and postoperative scarring are the most important determinants of the final intraocular pressure (IOP) and success after glaucoma surgery.[7,10,11] Individuals have different conjunctival healing/scarring responses that are related to a number of known factors, including previous ocular surgery, age, ocular inflammation, presence of neovascularisation and race. The use of anti-scarring agents to prevent post glaucoma filtering surgery scarring has been one of the major areas of advancement in glaucoma surgery. With recent evidence suggesting that target pressures should be lower than previously considered necessary,[12] successful modulation of the healing response after surgery has become critical. The use of anti-scarring agents to inhibit fibroblast replication and function is important in achieving early filtration as well as enhancing bleb survival.

MMC is effective at increasing the success of glaucoma surgery through its inhibition of the wound healing pathway, specifically through inhibi-

tion of fibroblast as well as endothelial growth and replication.[7,11]

In 1983, Chen et al.[13] were the first to use MMC in conjunction with pterygium surgery. Later, they also applied this drug subconjunctivally at the filtering site during trabeculectomy in high-risk eyes. Although there has been no general consensus regarding optimal dose and method of application, MMC has since been used with increasing frequency, not only in eyes at risk for bleb failure, but also in eyes traditionally considered to be at low risk for failure.[14] This practice has, in part, been driven by the desire to achieve lower target IOP, thereby increasing the chance to keep a stable visual field.[15]

In addition to its adjunctive use in primary trabeculectomy, with and without risk factors for failure, MMC has been used as adjunctive treatment in redo-trabeculectomy, combined cataract and glaucoma surgeries, congenital glaucoma surgery, glaucoma drainage implants and revision of failed filtering blebs.

Primary Trabeculectomy

During the last 3 decades, there have been numerous studies that assessed the success rate of MMC-augmented trabeculectomy. The dose of MMC has ranged from 0.1 to 0.5mg/mL; with the most commonly used concentration being 0.2mg/mL (0.02%).[14-22] Intraoperative exposure time has ranged from 2 to 5 minutes, and a variety of MMC-soaked sponges have been used to apply MMC between the globe and conjunctiva. The optimum dose for intraoperative application remains debatable; however, there is considerable evidence to indicate that higher doses correlate with higher complication rates.[16,17] Conversely, the minimum dose that retains efficacy is unclear, but is likely to depend upon the predilection for scarring in a given individual. Hence, Stone et al.[18] have suggested that a risk-factor grading system should be established preoperatively, based on the patient's risk of scarring, and that the exposure time to MMC should be adjusted accordingly. Although a similar strategy (varying the dose and/or exposure time) has been adopted by many glaucoma surgeons, a scientifically rigorous analysis of this approach has not been conducted.

Table II summarises several studies that used adjunctive MMC in primary trabeculectomy; most of them were retrospective in nature.[19-24] The few prospective studies were of short duration, with variable risk factors and patient demographics.[25,26] The surgical approach, the concentration of MMC used, the size, number and type of sponge used for application, and the duration of application, varied between and within studies.

Since the fibroblastic response is considered to be greater in the early postoperative period, one would expect a large number of early failures. However, data from studies with long-term follow-up have shown that fibrosis continues to occur even after 5 years.[23,24] The success rates with adjunctive MMC are definitely better than those with fluorouracil (5-FU), another potent anti-scarring agent.[23,26]

Most of the studies have emphasised an IOP of <21mm Hg as the main outcome measure. Although such IOP was traditionally considered successful, there is no evidence that glaucoma remains stable at that IOP.[15] With the understanding of the marked difference in susceptibility to the damaging effects of IOP, a target IOP that is tailored for each individual patient would be the ideal outcome measure. Preserving visual function, as indicated by stable visual acuity and visual fields, and incidence of complications are outcome measures that will give a clue to the postoperative quality of life. The retrospective study by Bindlish et al.,[19] which referred to some of these parameters, found that 83% of the patients who underwent standard trabeculectomy with MMC achieved the target IOP at 5 years. However, when surgical success was defined as IOP which is less than target IOP but >6mm Hg (hypotony), and when the parameter of loss of four or more lines of vision was also included in this definition, the percentages fell to 57.7%. Hypotony was more common in the group of patients who received a higher concentration of MMC (0.05%) than those with the lower concentration (0.03%).

The current data indicate that MMC significantly increases the success rate of trabeculectomy in eyes at high risk for failure. A dose of 0.02–0.04%, applied for 2–3 minutes, can be titrated to achieve the goal of target IOP for the individual patient.

Table II. Comparison of studies using intraoperative mitomycin C (MMC) in primary trabeculectomy

Study (year)	No. of eyes	Study design	MMC dose (%)	Outcome measures	Results (% pts)	Average follow-up	Study limitations
Lamping and Belkin[26] (1995)	80	Prospective, randomised	0.04	IOP reduction; repeated measures analysis	Lower IOP with MMC; significant linear trend over eight measurements	12mo	Short-term follow-up
Nuijits et al.[25] (1997)	25	Prospective	0.05	IOP <21mm Hg; 20% IOP reduction if preoperative IOP <21mm Hg	92%	12mo	Small sample size
Cheung et al.[21] (1997)	132	Retrospective	0.02–0.05	IOP <21mm Hg with no med	63%	3y	Retrospective, high loss of follow-up by 3y
				IOP <18mm Hg on one med	83%		
Perkins et al.[22] (1998)	68	Life table analysis	0.05	IOP <21mm Hg or 20% reduction in IOP	47% success at 3y; 70% success with medication	2–3y	High loss of follow-up
Casson et al.[20] (2001)	21	Retrospective, life table analysis	0.02	Complete success: IOP <21mm Hg without med	Complete success: 81%	5y	Retrospective, small sample size
				Qualified success: IOP <21 mm Hg with or without med	Qualified success: 90.5%		
Bindlish et al.[19]	123	Retrospective,	0.025–0.05	Incidence of complications:		5y	Retrospective
(2002)		non-comparative		hypotony: IOP <6mm Hg	42.3%		
				bleb leaks/blebitis	14.6%/5.7%		
				maculopathy	8.9%		
				endophthalmitis	0.8%		
				IOP ≤ target IOP	83% at year 5		
				med reduction			
Beckers et al.[24] (2003)	50	Retrospective	0.02	Postoperative IOP ≤15mm Hg	83% success in the 1st year; 60% in the 6th year	5y	Retrospective
				Stable visual fields	73.3% stable during follow-up		
Akarsu et al.[23] (2003)	36	Retrospective, comparative	0.04 vs 5-FU 0.1	IOP ≤21mm Hg with or without med	Success at 1y; MMC 82.3%, 5-FU 73.6%; success at 4y: MMC 60.5%, 5-FU 52.6%	4y	Retrospective

5-FU = fluorouracil; **IOP** = intraocular pressure; **med** = medication; **pts** = patients.

Table III. Comparison of studies using intraoperative mitomycin C (MMC) in combined cataract and glaucoma surgery

Study (year)	No. of eyes	Study design	MMC dose (%)	Outcome measures	Results (% pts)	Follow-up	Study limitations
Cohen et al.[29] (1996)	72	Prospective, double-blind, controlled	0.05 × 2.5 min vs placebo	IOP reduction	Low IOP compared with placebo	1y	Short follow-up
Carlson et al.[28] (1997)	29	Prospective, randomised, controlled	0.05 × 3.5 min vs placebo	IOP reduction (5 ≤ IOP ≥15mm Hg)	85% MMC, 67% placebo	20mo	Small sample size
				Postoperative med	0% MMC, 33.3% placebo		
Shin et al.[30] (1998)	197	Prospective, randomised, controlled	0.05 × 1, 3, 5 min vs placebo	Set target IOP	Significant IOP reduction with MMC in those with risk factors for failure; no risk factors – no MMC; one risk factor – 1 min; more than one risk factor – 3 min	24mo	
Shin et al.[31] (2002)	203	Retrospective, case control	0.05 × 1, 3, 5 min vs control	IOP reduction; visual field outcome	Better IOP control and stable fields with MMC	36mo	Nonprospective

IOP = intraocular pressure; **med** = medication; **pts** = patients.

Combined Cataract/Glaucoma Surgery

In combined surgery for the treatment of cataract and primary open-angle glaucoma, the use of adjunctive MMC achieves a significantly lower IOP than surgery without MMC.[27-32] Evidence suggests that combined surgery with MMC achieves similar IOP results as trabeculectomy alone without MMC, but may not be as successful as trabeculectomy with MMC.[27,33] However, in patients with visually disabling cataract and severe glaucomatous damage, combined surgery with MMC is recommended.[34]

The reason for the increased risk of fibrosis when trabeculectomy is performed at the same time as cataract surgery with small incisions remains unclear, but it may be related to the prolonged disruption of the blood-aqueous barrier after cataract surgery.[35,36] The results seem to be better in eyes that undergo phaco-trabeculectomy with foldable intraocular lens compared with standard extracapsular cataract extraction and trabeculectomy.[37,38]

The comparison between the different studies with adjunctive MMC in combined cataract and glaucoma surgery is presented in table III. All studies show an improved success rate with the use of MMC in combined procedure in eyes at risk for failure. Most of these studies have looked at IOP reduction as the primary outcome measure. In a large, prospective randomised trial, Shin et al.[30] showed that adjunctive MMC significantly improved the filtration outcome of the surgery in the group with risk factors for filtration failure. Further studies have demonstrated stable visual fields with the use of adjunctive MMC in combined surgeries.[31] A systematic Cochrane review on the use of MMC in combined cataract extraction and trabeculectomy found that there was significant IOP reduction with MMC in combined surgeries.[32]

The fact that combing cataract surgery with trabeculectomy appears to be a risk factor for failure of the glaucoma operation seems to justify the use of adjunctive MMC. The optimal dose and exposure time are not completely evaluated.

Congenital Glaucoma Surgery

The management of congenital glaucoma is primarily surgical. Glaucoma filtering surgery in children and young adults is often unsuccessful because of the aggressive wound healing response, presence of a thick Tenon's capsule and low scleral rigidity. The encouraging outcome of surgery with MMC in adults, the high potential to prevent scarring and the obvious difficulties in injecting MMC postoperatively in children make this drug an appealing intraoperative adjunct in congenital glaucoma surgery in children. Recent evidence suggests an improved success rate when MMC is used as adjunctive therapy for primary[39-43] and repeat surgery;[44] however, long-term follow-up is still required.

Glaucoma Drainage Devices

MMC has been increasingly used as an adjunct in glaucoma drainage device (GDD) surgery for the management of refractory glaucoma. The mechanism of filtration in an eye with a GDD is through the fibrous capsule that surrounds the plate and the degree of filtration is proportional to the overall surface of the capsule surrounding the plate.[45] There is considerable evidence that addition of MMC does not alter the outcome in patients undergoing non-valved GDD implantation and there is an increased incidence of complications.[45-48] In a recent randomised, controlled clinical trial, Costa et al.[49] have shown that MMC (0.05% for 5 minutes) had no effect on success rates of Ahmed glaucoma valve implantation. The complication rates were similar to those without MMC. The reasons for the lack of efficacy when used with a GDD remain unclear; although it is postulated that the presence of a foreign body, a constant stimulus for fibroblast proliferation, may later overcome the antiproliferative effects of MMC.[49]

Revision of Failed Filtering Blebs

Rather than performing a repeat procedure, which itself is an added risk for failure, investigators have tried to revise the filtering blebs by needling the scar tissue. MMC (0.04–0.05%) was used as adjunct for needle revision, either preoperatively as subconjunctival injection or intraoperatively. It appears to be an extremely effective way to revive failed filtrating blebs; however, none of these studies had a control group for comparison.[50-52] Although these reports do not provide conclusive evidence that needling with MMC is more effective than performing needling alone, given that any surgical intervention might increase the chances of scarring and fibrosis, the use of adjunctive MMC with needling seems justified.

2.1.2 Pterygium Surgery

Pterygium is an elastotic degeneration of the conjunctiva that produces fibrovascular tissue, which invades the superficial cornea. This ocular surface disease is common worldwide, with increasing prevalence in tropical areas.[53] Theories of the pathogenesis of pterygium have shown ultraviolet light exposure as a major causative factor.[54-56] It has been proposed recently that the initial biological event in pterygium pathogenesis is an alteration of limbal stem cells due to chronic ultraviolet light exposure.[57] Pterygium is often asymptomatic and does not need treatment. The most common indications for treatment are cosmetic appearance and chronic irritation. In addition, a pterygium can cause decreased vision when it is large, close to the visual axis or if it induces astigmatism.

The definitive treatment for pterygium is surgical resection but recurrence is the most common complication. The earlier techniques were based on removing the pterygium and leaving bare sclera.[53] However, this was associated with high recurrence rates of 30–90%.[58] Later modifications were based on using a conjunctival autograft, sutured to the area of excision. This was associated with a recurrence rate of 5–39%.[59-62] Other treatment modalities, such as radiotherapy, amniotic membrane transplantation and limbal conjunctival auto-transplantation, resulted in variable success rates.[63-65]

MMC was used as an adjunct to pterygium surgery as early as 1963 and is currently the most commonly used antimetabolite used in an attempt to reduce the recurrence rates in this surgery. It can be used intraoperatively or postoperatively, and the concentrations used range from 0.1 mg/mL (0.01%) to 1 mg/mL (0.1%).[62,63,66-79] The dosage of MMC and method of administration are significant variables affecting the success rate after pterygium excision. The type of pterygium also plays an important role in the final recurrence; recurrence rates are higher with recurrent pterygia than with primary pterygia.[53]

One of the earliest reports on postoperative use of MMC in pterygium surgery was by Murakami et al.[80] in 1967. Studies have shown that postoperative instillation of 0.02% MMC, twice a day for 5 days, is effective and safe in the treatment of primary pterygium.[66] Higher concentrations were reported to induce toxicity and irreversible damage to the surrounding ocular tissues,[67] as well as sight-threatening complications.[68,69] Frucht-Pery and Ilsar[70] performed a randomised trial and found that a low concentration of MMC (0.01%), used for 5 days postoperatively, was as effective in reducing recurrence and had no major complications. Table IV summarises the various studies on postoperative use of MMC. With complications occurring as late as 33

months,[69] the use of postoperative MMC may not be considered safe, as the surgeon has no direct control over the concentration, duration or location of MMC application.

This has led to extensive research on the use of MMC as intraoperative adjunctive therapy in pterygium surgery (table V).[71-79,81] All studies show a statistically significant decrease in recurrence rates with the use of adjunctive MMC. Studies comparing intraoperative and postoperative MMC in pterygium surgery found that recurrence rates were not statistically different according to the type of application.[74,75,79]

Investigators have compared low-dose MMC with conjunctival autografts, with or without limbal stem cell transplantation, and amniotic membrane transplantation, and found that the recurrence rates were similar to or better than MMC.[62,63,81] However, these techniques are time consuming, and require good surgical expertise and significant manipulation of the conjunctiva, which may deplete the stem cell reserves of the cornea. Compared with these, MMC is much simpler to use and, in case of recurrence with MMC, there will be enough conjunctiva and stem cells for re-treatment. MMC can also be used as adjunctive therapy with conjunctival autografts and amniotic membrane transplantation in primary and recurrent pterygia, with lower recurrence rates.[63,82]

2.1.3 Lacrimal Surgery

Dacryocystorhinostomy

Addeo Toti first described the technique of external dacryocystorhinostomy (DCR) in 1904.[83] A mucosal anastomosis, with suturing of the mucosal flaps, was later described by Dupuy-Dutemps and Bourguet.[84] With the exception of minor alterations, external DCR is still performed in much the same way. The success rate has improved over the years as a result of better preoperative assessment, including radiological investigation of the nasolacrimal system, the use of absorbable and less irritant suture materials, and improved instruments and anaesthetic procedures.

The success rate of DCR has been reported at between 80% and 99%, depending on the surgeon's experience.[85,86] A review of the literature reveals an average failure rate of 9.4%.[87] The two most frequent causes of DCR failure are obstruction of the common canaliculus and closure of the osteotomy site.[88,89] From the literature, it is clear that fibrous tissue growth, scarring and granulation tissue formation during the healing process will decrease or compromise the created surface area of the osteotomy site, leading to surgical failure. The same healing process will also promote adhesion of the osteotomy to the turbinate and septum, or induce obstruction of the common canaliculus.[90] Linberg et al.[91] have shown that an appropriately large osteotomy made during surgery can narrow down to a final size of approximately 2mm as a result of tissue growth and scarring. The failure rate of DCRs may become much lower if fibrous proliferation at the osteotomy site and at the anastomosed flaps is reduced by adjunctive therapy.

MMC has been applied over the osteotomy site and the anastomosed flaps to suppress fibrous proliferation and scar formation. The concentrations

Table IV. Comparison of studies on pterygium surgery with postoperative mitomycin C (MMC)

Study (year)	No. of eyes	Study design	Type of pterygium (no. of eyes)	MMC dose (%)	Duration of treatment	Follow-up period	Recurrence rate	Study limitations
Singh et al.[67] (1988)	62	Prospective, randomised	Primary (48) recurrent (14)	0.1 vs 0.04 vs placebo	2 wks	23 wks	2.3% with MMC, 88.9% with placebo; high complication rate for 0.1%	Short follow-up
Hayasaka et al.[66] (1988)	99	Prospective, randomised	Primary	0.02 vs excision vs radiation vs 0.04	5d	3–8y	Reduction in recurrence with 0.02% MMC compared with no MMC	
Frucht-Pery and Ilsar[70] (1994)	75	Prospective, randomised, blinded	Primary (56) recurrent (19)	0.01 vs 0.02 vs β irradiation	5d	15mo	8% with 0.01; 4% with 0.02; 20% with β irradiation	Short follow-up

Table V. Comparison of studies on pterygium surgery with intraoperative mitomycin C (MMC)

Study (year)	No. of eyes	Type of pterygium (no. of eyes)	Study design	MMC dose (%)	Groups compared	Follow-up period (mo)	Recurrence (%)	Study limitations
Frucht-Pery et al.[71] (1994)	40	Primary, recurrent	Prospective, randomised	0.02	1) MMC 0.02% 2) NaCl 0.9%	6–15	1. 5 2. 45	Short follow-up
Cardillo et al.[74] (1995)	227	Primary	Prospective, randomised	0.02 vs 0.04	1) 0.02% 3 min 2) 0.04% 3 min 3) 0.02% 7d 4) 0.04% 14d	28	1. 6.66 2. 4.08 3. 4.26 4. 4.44	
Caliskan et al.[73] (1996)	43	Primary	Prospective, randomised	0.04	1) Intraoperative 2) Postoperative	10.3	1. 5.3 2. 4.2	Short follow-up
Frucht-Pery et al.[72] (1996)	81	Primary (75), recurrent (6)	Prospective, randomised	0.02	1) 0.02% 5 min 2) NaCl 0.9%	12–28	1. 4.1 2. 46.9	
Manning et al.[75] (1997)	56	Primary	Prospective, randomised	0.02 vs 0.04	1) 0.02% 7d 2) 0.04% 3 min	16	1. 21.1 2. 10.5	Short follow-up
Lam et al.[76] (1998)	180	Primary (145), recurrent (35)	Prospective, randomised	0.02 vs 0.04	1) 0.02% 3 min 2) 0.04% 3 min 3) 0.02% 5 min 4) 0.04% 5 min	1. 20 2. 20 3. 30 4. 30	Primary/recurrent 1. 37.9; 66.7 2. 17.9; 42.9 3. 6.9; 14.3 4. 7.1; 14.2	
Cheng et al.[77] (2001)	96	Primary (38), recurrent (58), MMC (26), CAT (32)	Prospective	0.02	1) 0.02% 30 sec primary 2) 0.02% 30 sec recurrent 3) CAT recurrent	27–40	1. 7.9 2. 19.2 3. 6.3	
Donnenfeld et al.[78] (2003)	36	Primary (20), recurrent (16)	Prospective, non-comparative	0.015	Subconjunctival injection 1mo before excision	24	6%	Short follow-up
Young et al.[81] (2004)	115	Primary	Prospective, randomised	0.02	MMC LCAU	12	15.9; 1.9	Short follow-up
Raiskup et al.[79] (2004)	99	Primary	Prospective, non-comparative	0.02 vs 0.01	1) 0.02% 5 min 2) 0.01% or 0.02% twice daily for 5d	10y	6.9% at 1y	>50% lost to follow-up

CAT = conjunctival autograft; **LCAU** = limbal conjunctival autograft; **NaCl** = saline solution.

used in various lacrimal surgeries range from 0.02% to 0.04%. Kao et al.[92] first reported the use of MMC in a series of 14 patients who underwent DCR with and without MMC. At 6-month follow-up, the osteotomy size was significantly larger in patients in whom MMC was used compared with controls. These findings were supported in a prospective randomised trial which showed an increase in both ostium size and patency with the use of MMC during external DCR.[93] However, other studies did not show any significant increase in success rate with the use of MMC in DCR.[90,94]

Although there are limited data and a lack of long-term prospective studies on the efficacy of adjunctive MMC in redo-DCR for recurrent lacrimal drainage system obstruction,[95] it is commonly used in daily practice. MMC has also been used in endoscopic DCRs with variable success rates.[96,97]

Other Lacrimal Surgeries

Silicone intubation of the lacrimal drainage system is indicated in patients with congenital nasolacrimal duct obstruction, and in patients with acquired nasolacrimal duct obstruction and dacryocystitis.[98,99] MMC has been used as an adjunct in this surgery with no definite improvement in success rate.[100]

Stenosis of the lacrimal punctum can be caused by a variety of factors and various treatment modalities have been described. Lam and Tessler[101] were the first to report the successful use of MMC as adjunct to repeat punctal snip procedures. Ma'luf et al.[102] reported their experience in 50 patients, and have shown that MMC is a safely used and effective adjuvant in punctual snip procedure.

2.1.4 Refractive Surgery

Excimer laser photorefractive keratectomy (PRK) is commonly used to correct myopia, hyperopia and astigmatism.[103] Recently, it was widely replaced by laser *in situ* keratomileusis (LASIK), which is associated with less postoperative discomfort and corneal haze.[104] The use of topical corticosteroids is probably the most common treatment to prevent corneal haze but this has not shown significant efficacy in controlled studies.[105,106] Moreover, when used for longer periods, it can result in steroid-induced ocular complications such as cataract, glaucoma and infections. A number of anti-inflammatory agents have been investigated as adjunctive treatment to corneal laser refractive surgery, including nonsteroidal anti-inflammatory agents, plasmin inhibitors, vitamins A (retinol) and E (tocopherol), amino acids, amniotic membrane and ubiquinone Q10 (ubidecarenone).[106,107] However, the available data on the efficacy of these treatments are based on case reports or limited series and not on controlled clinical trials.

The first application of MMC as a modulator of corneal wound healing after refractive surgery was suggested by Talamo et al.[108] in rabbit eyes. Histopathological examination strongly indicated that MMC inhibited subepithelial collagen synthesis. Further animal studies have demonstrated similar results.[109,110]

Majmudar et al.[111] evaluated the effectiveness of MMC (0.02%) in reducing corneal haze in patients who had undergone refractive corneal surgery. In all patients, the cornea remained clear with no recurrence throughout a mean follow-up period of 14 months. Other larger studies have shown comparable results.[112] Gambato et al.[113] evaluated the role of topical MMC in PRK where one eye of each

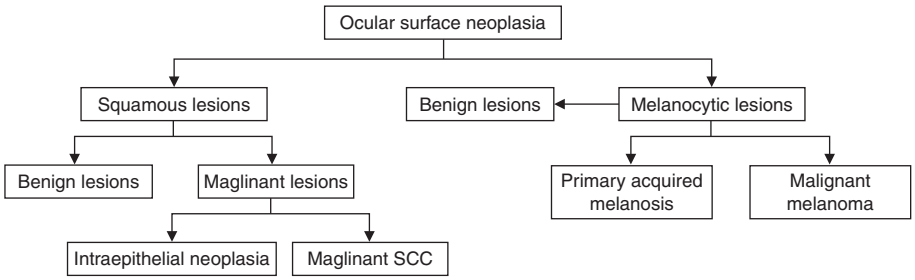

Fig. 1. The subdivision of the ocular surface neoplasias. **SCC** = squamous cell carcinoma.

Table VI. Comparison of studies on mitomycin C (MMC) as treatment for ocular surface squamous neoplasia

Study (year)	No. of eyes	Study design	MMC dose (%)	Duration of treatment	Follow-up (mo)	Outcome (tumour regression; %)	Study limitations
Wilson et al.[126] (1997)	7	Retrospective	0.04	qid for 7d, alternate weeks	9	85.5	Retrospective, small sample size
Heigle et al.[127] (1997)	3	Case reports	0.02–0.04	3–20wk	6–9	100	Small sample size
Frucht-Pery et al.[128] (1997)	17	Clinical case series	0.02–0.04	qid for 7–28d	6	64.7 after one cycle; 82 after two cycles	Short-term follow-up
Rozenman and Frucht-Pery[129] (2000)	8	Case reports	0.02–0.04	qid for 14d	24–44	37.5 after one cycle; 87.5 after two cycles	Small sample size

qid = four times a day.

patient was randomised to receive MMC and the other received placebo. At 18-month follow-up, there was no haze in MMC-treated eyes, whereas 20% of control eyes had significant haze. MMC has also been shown to be a useful adjunctive therapy for the prevention of haze when applying surface excimer laser therapy to a cornea following LASIK flap complications.[114,115]

From the available data, it is evident that topical MMC may be effective in the prevention of corneal haze in refractive surgeries, but long-term follow-up is lacking.

2.1.5 Surgery for Ocular Cicatrisation

Extensive scarring of the conjunctiva is found in severe cicatricial ocular surface diseases such as mucous membrane pemphigoid (MMP), Stevens-Johnson syndrome (SJS), chemical and thermal burns, multi-recurrent pterygia and eyes that have undergone multiple surgeries. Cicatrisation prevents the formation of an adequate tear meniscus, interferes with eyelid blinking and closure, and may result in trichiasis, thus further compromising the ocular surface. Cicatrisation involving the muscles can cause restriction of ocular movements and diplopia.

Ocular cicatrisation is difficult to treat, and the management of MMP usually involves systemic therapy with immunomodulators such as methotrexate, cyclophosphamide, intravenous immunoglobulins and mycophenolate mofetil, with or without dapsone to control inflammation and prevent progression to irreversible blindness. This is supplemented by surgical intervention in advanced disease.[116] In these patients, ocular surface reconstruction surgery has a very high chance of failure because of ongoing chronic inflammation and fibrosis. Donnenfeld et al.[117] evaluated the efficacy of subconjunctival MMC in MMP by giving subconjunctival MMC (0.02%) preoperatively in the eye with more severe disease: after 2 years, 88% of patients showed quiescence of their MMP in the treated eye compared with 55% of control eyes. Another study found subconjunctival MMC to be effective in preventing progression of conjunctival cicatrisation in patients with MMP.[118]

In addition to preventing the progression of cicatrisation, restoration of a deep fornix and tear meniscus are important prerequisites to achieve successful reconstruction by subsequent limbal stem cell transplantation. Amniotic membrane transplantation has been shown to be better than mucous membrane grafts in restoring a deep fornix after symblepharon lysis.[119] Intraoperative MMC (0.04%) when used as adjunct in fornix reconstruction surgery, along with amniotic membrane graft, helps amniotic membrane restore a deep fornix after symblepharon lysis, even in eyes that have a failed mucous membrane graft.[120,121]

2.2 Ocular Malignancy

Ocular surface neoplasia (OSN) consists of a number of benign and malignant lesions of the conjunctiva and cornea. On the basis of the cell of origin they are subdivided into squamous and melanocytic lesions (figure 1). The malignant squamous neoplasia, or ocular surface squamous neoplasia (OSSN),

Table VII. Comparison of studies on mitomycin C (MMC) as adjunct to surgery in ocular surface squamous neoplasia

Study group (year)	No. of eyes	Type of study	MMC dose (%)	Duration	Follow-up (mo)	Outcome (tumour regression)	Study limitations
Akpek et al.[130] (1999)	4	Case reports	0.02	tid for 2 wks	20	100%	Small sample size
Siganos et al.[131] (2002)	8	Retrospective	0.02	5 min intraoperative	16	87.5%	Small sample size
Kemp et al.[134] (2002)	11	Retrospective	0.04	qid for 2 wks and intraoperative	6–36	Good result	Small sample size
Chen et al.[135] (2004)	27	Prospective, non-comparative	0.04	qid for 1wk, 2–3 cycles	27	No recurrence	

tid = three times a day; **qid** = four times a day.

are classified into intraepithelial neoplasia and invasive squamous cell carcinoma. Melanocytic neoplasms include premalignant primary acquired melanosis (PAM) and malignant melanoma.[122]

Complete surgical excision with tumour-free margins is the gold standard in treatment of ocular surface neoplasias.[123] Nevertheless, in diffuse and extensive involvement, it may not be possible to achieve complete excision of the tumour.

2.2.1 Ocular Surface Squamous Neoplasias

OSSN, also known as conjunctival-corneal intraepithelial neoplasia (CCIN), is associated with potential ocular and systemic morbidity and even death. The reported recurrence rate after surgical excision of OSSN is 15–52%, with the major risk factor being inadequacy of excision margins.[124] Conversely, removal of excess conjunctiva results in cicatricial changes, ocular motility dysfunction and irregular astigmatism from corneal involvement. This has made the use of adjunctive therapies increasingly popular. Radiotherapy, cryotherapy and immunotherapy were actively investigated in the treatment of OSSN.

Chemotherapy with topical antimetabolites has revolutionised the management of OSSN. Frucht-Pery and Rozenman[125] in 1994 were the first to report the use of MMC in intraepithelial neoplasias. Administration of topical MMC 0.02% for 2 weeks was found to be an effective treatment for corneal intraepithelial neoplasia that involves the visual axis. Since then, there have been numerous studies confirming the benefits of MMC in OSSN.[126-129] The concentration of MMC used ranged from 0.02% to 0.04%. The comparison between the studies where topical MMC was used as treatment for OSSN is given in table VI. All the studies show good response to treatment with no major adverse effects.

This has led to investigating the use of topical MMC as adjunct to surgery for OSSN.[130-135] The various studies that have used MMC as adjunct to surgery in OSSN is shown in table VII. All studies have shown that MMC is a very effective adjuvant for surgical treatment of OSSN. Even smaller doses of MMC have been found to reduce recurrence.[136]

2.2.2 Primary Acquired Melanosis with Atypia

PAM usually presents in the sixth or seventh decade of life and is more common among Caucasians.[137,138] PAM is a unilateral, mostly unifocal, flat, brown conjunctival lesion. PAM without cellular atypia has minimal potential for malignancy, whereas when atypia is present, the estimated rate of progression to melanoma is as high as 46.4%.[137] Local excision with cryotherapy has been the most common treatment for PAM especially if biopsy shows atypia.[139] The adverse effects are similar to those with surgical excision of OSSN. Since the first report in 1996,[140] there have been a number of studies investigating the use of MMC as primary modality and as adjunct to localised surgery in PAM with atypia. The concentration of MMC used is the same as that for OSSN (0.02–0.04%). Pe'er and Frucht-Pery[141] presented a retrospective analysis of 12 patients with PAM with atypia. All patients were treated with two to five courses of topical MMC four times a day. At 1-year follow-up, all lesions had resolved.

2.2.3 Conjunctival Melanoma

Malignant melanoma of the conjunctiva is a rare ocular malignancy. Its incidence is 0.2–0.8 million in White populations.[142] It is potentially lethal with an average 10-year mortality of 30%. Although, the preferred management of conjunctival melanoma is total surgical excision,[143] complete excision is not always possible. Cryotherapy applied to the margins and base of the excised tumour has reduced the risk of local recurrence.[144] More recently, topical MMC (0.04%) has been used as adjuvant after surgical excision in extensive conjunctival melanomas.[134] Data from long-term follow-up examinations of patients with conjunctival melanoma are limited; however, retrospective studies have not shown any benefit with use of topical MMC compared with local excision followed by irradiation or cryotherapy.[145]

Evidence that NAD(P)H:quinone oxidoreductase (NQO1) plays an important role in the bioactivation of MMC has led Wilson et al.[146] to examine pathological specimens of conjunctival melanoma and PAM with atypia for NQO1 by immunohistochemistry. They found that all tumours stained positively for NQO1. This evidence supports the use of MMC in these tumours. Other studies have also evaluated topical MMC chemotherapy and found regression of conjunctival melanoma, although conjunctival and orbital recurrences were reported on histopathological examination.[147]

3. Complications

3.1 Ocular Surgery

Although MMC improved the success rate of ocular surgeries in terms of long-term IOP control, reduction of pterygium recurrence, reduction in corneal haze after refractive surgery, and probable success in surgeries on the lacrimal apparatus, it has also increased the risk of complications. This is because of its prolonged cytological toxicity. The reported sight-threatening complications are mainly related to its use as an adjunct in glaucoma filtering surgeries and pterygium surgeries. Its use in the other ocular surgeries has only been associated with minor reversible complications. The adverse effects of MMC are not limited to the immediate postoperative period.[68,69,148-150] MMC is cytotoxic to the fibroblasts and vascular endothelial cells,[151] and the effect on vascular endothelial cells may result in ischaemia of the conjunctiva and sclera, and related complications.

MMC administration during glaucoma surgery often leads to thin-walled avascular blebs. These blebs, although better in terms of success of filtration, are potentially associated with aqueous leaks and subsequent development of endophthalmitis.[148] Endophthalmitis is a severe intraocular infection that is a dreaded complication of any intraocular surgery and can result in permanent visual loss. The risk of endophthalmitis after filtration surgery with successful blebs can persist for months and years.[152,153] Although *Streptococcus* and *Staphylococcus* species are the most common causative orga-

Table VIII. Complications associated with the use of mitomycin C in ocular surgery

Complication
Glaucoma
Corneal epithelial toxicity
Conjunctival wound leaks
Bleb leaks
Blebitis
Hypotonic maculopathy
Choroidal effusion
Cataract formation/progression
Shallow anterior chamber
Suprachoroidal haemorrhage
Endophthalmitis
Retinal vein occlusion
Hyphaema
Upper eyelid retraction
Retinal haemorrhage
Bullous keratopathy
Pterygium
Ocular pain
Foreign body sensation
Photophobia
Non-healing conjunctival epithelial defect
Superficial scleral melting
Scleral thinning/ectasia/calcification
Corneal epithelial toxicity
Corneal dellen/ectasia
Corneal perforation
Corneoscleral ulceration
Conjunctival cyst/granuloma
Symblepharon
Secondary glaucoma
Other ocular surgeries
Foreign body sensation
Photophobia
Non-healing conjunctival epithelial defect
Corneal epithelial toxicity

nisms identified with delayed-onset bleb-associated endophthalmitis,[148,149,153] fungi such as *Lecythophora mutabilis* have also been reported.[152] In a large retrospective analysis of 609 eyes, Greenfield et al.[149] reported that the incidence of bleb-associated endophthalmitis was higher in those with adjunctive MMC than those without the use of antifibrotic agents. Furthermore, the thin-walled blebs lead to low outflow resistance and subsequent overfiltration, which may then lead to hypotony. The consequences of ocular hypotony include choroidal effusion, choroidal haemorrhage, maculopathy, shallowing of the anterior chamber, corneal decompensation, disruption of the blood-aqueous barrier and cataract formation.[7]

The complications of MMC, when used as an adjunct in pterygium surgery, can range from mild discomfort to scleral ulceration and symblepharon formation.[68,69,150,154] The complication rate is higher with higher concentrations of MMC and with postoperative rather than intraoperative use. Late-onset scleritis has been reported in eyes that had bare sclera surgery with MMC.[155] Covering the bare sclera with a conjunctival sliding graft after intraoperative MMC is thought to reduce the rate of complications. However, even low concentrations of MMC (0.02% for 3 minutes) and a sliding conjunctival graft can still result in serious ocular complications such as perforation.[150]

When used as adjuncts in other surgeries, the complications were limited to transient and mild keratoconjunctivitis. The complications associated with the use of adjunctive MMC in ocular surgery are as listed in table VIII.

Judicious use of MMC, taking into consideration the concentration and the duration of exposure, will help to minimise the complications. Thorough and meticulous irrigation of the site of contact with saline is crucial. Whenever MMC is used as adjunctive therapy in ocular surgeries, the treating surgeon should adopt a high index of suspicion regarding the potential complications and counsel patients accordingly.

Table IX. Complications associated with the use of mitomycin C (MMC) in ocular malignancy

Limbal stem cell deficiency
Punctal stenosis
Ocular irritation
Conjunctival hyperaemia
Tearing
Punctate keratopathy
Blepharospasm
Corneal oedema
Ocular pain

3.2 Ocular Malignancy

Unlike in its use as adjuncts in glaucoma surgery and pterygium surgery, the complications associated with the use of MMC in ocular malignancies are very mild and transient. Among the many complications listed in table IX, limbal stem cell deficiency and punctal stenosis are the most significant complications associated with the treatment of OSSN.[156,157]

In PAM with atypia, the adverse effects are mainly acute transient conjunctival injection, chemosis and keratitis. One study noted secondary changes similar to the changes described in the urothelium after intravesical use of MMC. These changes are important to recognise and to differentiate from recurrent neoplasm.[158] In conjunctival melanoma, MMC chemotherapy has been reported to cause intumescent cataract.[159]

4. Future and Experimental Ocular Treatment Options

4.1 Strabismus Surgery

The widespread use of MMC in reducing fibrosis and scarring, and the relatively innocuous adverse effects, have prompted investigators to use MMC in strabismus surgeries to reduce the fibrosis and restriction of ocular movements. An experimental study in rabbits was the first published report that indicated that topical MMC exposure may inhibit scarring in strabismus surgery without inhibiting muscle reattachment.[160] Other clinical studies have shown similar results.[161]

4.2 Orbital Implant Surgery

Orbital implants are used in the restoration of anophthalmic socket after enucleation and evisceration. The hydroxyapatite implant is an ocular motility implant designed to provide natural movement of

the artificial eye and this is maximised when the implant is coupled to the prosthesis using a peg.[162] However, peg extrusion has been reported to occur in 25–30% of patients. In an animal study, serial histopathological changes within the drill hole with the use of MMC were studied. In the groups treated with 0.05% MMC, all the motility pegs were maintained in position with the holes at ample depth and width, whereas in the control group, all the motility pegs were extruded showing occluded holes. Higher concentration was associated with complications.[163]

4.3 Proliferative Vitreoretinopathy

Limited *in vivo* data indicate that MMC may have clinical application in the treatment of proliferative vitreoretinopathy (PVR).[164]

4.4 Optic Nerve Sheath Fenestration

Optic nerve sheath fenestration or decompression (ONSD) is employed to treat benign intracranial hypertension. A reported failure rate of up to 35% may be related to scarring of the nerve sheath by proliferation of epidural fibroblasts at the site of the incisions or fenestration.[165] On the basis of experience with MMC in glaucoma surgery, it has been used as an adjunct to ONSD to decrease the incidence of fibrotic obstruction of the fenestration site.[166] However, the toxic effects of the drug on the optic nerve are still not clear. An experimental study has shown that the application of MMC to the optic nerve has a dose-dependent toxic effect in the short-term post-surgical follow-up period in rabbit eyes. However, the extent was not obvious on histopathological examination of the nerves.[167]

4.5 Posterior Capsular Opacification

Opacification of the posterior capsule is the most common postoperative complication of extracapsular cataract surgery. Although easily managed by laser capsulotomy, various drugs have been used intraoperatively in the prevention of posterior capsular opacification (PCO). One of the earliest studies on rabbits used a solution containing MMC for hydrodissection and found that it was more effective than heparin.[168] Shin et al.[169] have noted that intraoperative subconjunctival MMC application during combined glaucoma and cataract surgery has a beneficial effect of inhibiting PCO after combined surgery. They hypothesised that when MMC (0.05% for 3 minutes) was used, the aqueous MMC concentration was enough to inhibit the lens epithelial cell proliferation to result in a decrease in PCO.

4.6 Vernal Keratoconjunctivitis

Short-term, low-dose, topical MMC use has recently been described in the acute exacerbation periods of patients with severe vernal keratoconjunctivitis (VKC) refractory to conventional treatment.[170] Some investigators have also found topical MMC to be more effective than topical azelastine in the treatment of allergic conjunctivitis both in terms of relief of symptoms and resolution of signs.[171] MMC as an adjunct to papillary resection in patients with severe VKC reduces recurrence of corneal complications.[172]

5. Conclusion

MMC, which undergoes metabolic reductive activation, has various oxygen tension-dependent cytotoxic effects on cells, including the cross-linking of DNA. In ophthalmic use, it is principally used to inhibit the wound healing response and reduce scarring of surgically fashioned ostia. Hence, it has been used as adjunctive therapy in various ocular surgeries, such as glaucoma filtering surgeries, surgical management of pterygia, dacryocystorhinostomy, corneal refractive surgery and surgeries for ocular cicatrisation. MMC has improved the surgical success rates; however, sight-threatening complications may occasionally occur. In addition, it has been used as an adjunct in the treatment of OSSN, PAM with atypia and conjunctival melanoma. Its potential use in other ocular conditions, such as traumatic proliferative vitreoretinopathy, strabismus surgery orbital implant surgery, ONSD and VKC, has made MMC a very important drug if used judiciously in ophthalmic practice.

Acknowledgements

No sources of funding were used in the preparation of this manuscript. The authors have no potential conflicts of interest directly related to the contents of this article.

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