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Uses and complications of mitomycin C in ophthalmology

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Mitomycin C is a chemotherapeutic agent that acts by inhibiting DNA synthesis. Its use and application in ophthalmology has been increasing in recent years because of its modulatory effects on wound healing. Current applications include pterygium surgery, glaucoma surgery, corneal refractive surgery, cicatricial eye disease, conjunctival neoplasia and allergic eye disease. Although it has been used successfully in these conditions, it has also been associated with significant complications. This article reviews the current trends and uses of mitomycin C in the eye and its reported complications.

Keywords: conjunctival neoplasia, corneal haze, glaucoma, hypotony, mitomycin C, pterygium, refractive surgery, scleral necrosis, trabeculectomy

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1. Introduction

Mitomycin C (MMC) is an antitumour antibiotic that was first isolated from *Streptomyces caespitosus* by Wakaki *et al.* [1] in 1958. It is an alkylating agent and, like other alkylators, has a mechanism of action similar to radiation [1,2]. It inhibits DNA synthesis primarily during the late G1 and S phases, but is essentially not cell cycle specific. Cellular RNA and protein synthesis are also affected at high concentrations. Without the correct DNA and RNA, cell migration and mitosis are inhibited. This results in a decreased rate of cell proliferation. Kunimoto and Mori [3] first reported the use of MMC in the eye to treat pterygia in 1963. It has since become increasingly popular in ophthalmology because of its properties as a wound-healing modulator. As well as being used to treat pterygia [4,5], it is also used in glaucoma drainage surgery [6-8], corneal and conjunctival dysplasia and neoplasia [9,10], allergic eye disease [11] and as a measure to prevent and treat haze formation in corneal refractive surgery [12-14].

However, MMC is also associated with potentially sight-threatening complications, including keratitis, corneal melting, scleral melting, hypotony and endophthalmitis [15-18]. An important consideration is that complications may arise months, and sometimes years, after the initial application. Therefore, MMC needs to be used cautiously with consideration given to the immediate and long-term possible complications.

2. Specific indications and safety concerns

2.1 Pterygium surgery

A pterygium is a fibrovascular growth of degenerative conjunctival tissue that grows across the limbus and invades the cornea. The main indication for removal is decreased visual acuity. This can be as a result of growth of the pterygium into the visual axis, induced astigmatism or disruption to the precorneal tear film [5,18]. Although pterygium removal is relatively straightforward, the main problem facing ophthalmologists has been recurrence, with rates as high as 70% [19]. Strategies have, therefore, evolved to try and reduce this recurrence rate with adjunctive MMC becoming an increasingly popular option.

MMC was first used in 1963 for pterygia [3] and there have been many reported cases since, with recurrence rates as low as 0.5% (range: 0.5 – 16%) [3-5,20-22].

The mechanism of action of MMC in the prevention of recurrence seems to be its inhibitory effect on fibroblast proliferation at the level of the episclera. This prevents the development of fibrosis and aggressive wound healing that are responsible for pterygium recurrence [21-23].

Although many studies have shown the effectiveness of MMC in preventing recurrence, serious complications have also been reported, which is why many ophthalmologists are reluctant to use it in all cases of pterygia [16,17].

Known complications, ranging from mild to sight-threatening, include punctate keratitis, chemosis, delayed conjunctival wound healing, scleral melting, corneal melting, iritis and sudden onset of mature cataract [16,17,24,25].

When MMC is applied to the eye following excision of the pterygium, it is applied by means of an MMC soaked swab and left in contact with bare sclera for a variable time period, usually up to a maximum of 5 min. The concentration is also variable with some ophthalmologists using 0.02% and others using higher concentrations [20,22,25].

At present, there is no consensus on concentration and duration of exposure to MMC. However, there is evidence suggesting that the use of lower concentrations (i.e., 0.02%) are associated with less complications and are still effective in preventing recurrence [24,25].

Long-term data regarding the safety of MMC in pterygium surgery is still needed. Solomon *et al.* [24] reported no complications with a follow-up period of 6 years in their small series and emphasised the importance of careful patient selection and meticulous attention to surgical technique. Longer follow-up data are lacking in the literature.

2.2 Glaucoma surgery

Glaucoma is a sight-threatening condition that causes damage to the optic nerve, usually secondary to raised intraocular pressure. When medical treatment fails, surgery is the next step and the mainstay of surgical treatment is a trabeculectomy. This involves creating a channel from the aqueous humor to the subconjunctival space. The problem with this procedure is that long-term success in terms of lowering intraocular pressure can be difficult to achieve due to the wound healing response of the eye. This is especially true of patients that have been on long-term topical medications, have had previous surgery, have a history of uveitis or are of Afro-Caribbean ethnicity [6,26].

With the introduction of MMC-augmented trabeculectomy in the early 1990s, long-term intraocular pressure control has improved through delayed wound healing resulting from inhibition of fibroblast proliferation [6-8,27].

Although MMC is now commonly used in glaucoma surgery, controversy as with its use in pterygium surgery still exists regarding the optimum concentration and exposure time [28,29]. Furthermore, better intraocular pressure control with adjunctive use of MMC comes at a price with many reported complications. The complications can be early or late and these include induction of corneal astigmatism, thin atrophic blebs and leaking blebs with subsequent endophthalmitis and hypotony [27,29,30]. The latter two complications are particularly sight threatening and difficult to treat. There is some evidence to suggest that complications are more likely when higher concentrations of MMC are used [31,32].

Bindlish *et al.* [29] looked at 5-year results in 123 patients following trabeculectomy using MMC 0.25, 0.33 or 0.5 mg/ml at an exposure time of 0.5 – 5 min. They found significant lowering effects of intraocular pressure at 5 years, but with a high-delayed incidence of hypotony. However, dose and duration of MMC did not appear to have a direct correlation with regards to incidence of complications.

Follow-up data over a longer period than 5 years are lacking in the literature.

2.3 Corneal refractive surgery

Excimer laser photorefractive keratectomy (PRK) has become a common technique to correct refractive errors [33-35]. However, because of its side effects, namely slow visual recovery, discomfort in the early postoperative period and corneal haze, it has been widely replaced by laser *in situ* keratomileusis (LASIK) [36,37].

Then again, in patients with high myopia, LASIK is often contraindicated as it cannot be performed safely without comprising corneal structural integrity and, therefore, the final visual outcome [38]. In these cases, PRK is the preferred treatment. However, high myopia corrected with PRK often leads to haze formation in a high percentage of cases with subsequent loss of vision [39,40].

Haze formation is thought to be due to subepithelial fibrosis as a result of abnormal activation or proliferation of stromal keratocytes following laser ablation. In recent years, topical MMC has been increasingly used in the prevention and treatment of haze formation, the rationale being its inhibitory effects on human keratocyte proliferation as well as causing keratocyte apoptosis [12-14,41].

There have been several prospective, masked randomised studies demonstrating the effectiveness of MMC in reducing haze formation as well as demonstrating its safety in corneal refractive surgery. Carones *et al.* [42] gave a single intraoperative dose of MMC (0.02% concentration) via a soaked microsponge for 2 min over the ablated area of cornea. In the control group (eyes that did not have MMC), 63% (19/30) developed significant haze formation compared with no eyes developing haze formation in the study group (30 patients). They also showed better refractive and visual outcomes in the study group. In addition, they reported no complications in their 6-month follow-up period. Furthermore, they evaluated the corneal endothelium in 14 study-group eyes and showed no differences with control-group eyes.

Gambato *et al.* [43], in their randomised series of 72 eyes, showed that in untreated eyes, there was haze development in

20% compared with 0% of eyes that had prophylactic MMC. They also used a concentration of 0.02% for 2 min and reported no complications in their follow-up period (mean 18 months; range: 12 – 36 months). In addition, they could not show any morphological change in the corneal endothelium or epithelium in study-group eyes compared with control-group eyes at 12 and 36 months postoperatively.

Although these two studies did not report any damage to the endothelium, Morales *et al.* [44] recently published their study aimed specifically at determining whether or not MMC caused endothelial damage. In their prospective trial, they report 18 eyes of 9 patients, 1 eye of each patient was randomised to receive MMC following laser ablation and the other received balanced salt solution. Endothelial cell count in the control group (eyes receiving balanced salt solution) showed no difference to preoperative levels. However, endothelial cell count in the MMC group (n = 9) showed a mean 14.7% reduction at 1 month and an 18.2% reduction at 3 months, which was statistically significant. The numbers were small in this trial, but nevertheless, the findings were extremely concerning, especially considering that they also used a very low concentration of MMC (0.02%) and application time was only 30 s.

In addition to the findings of Morales *et al.* [44], some concern over MMC use has also been raised by animal studies. Chang [45] showed that a single-dose application of MMC on the corneal surface caused corneal oedema and endothelial apoptosis in rabbit eyes, and suggested its cautious use in humans. Torres *et al.* [46] showed that MMC was detectable in the anterior chamber of hen eyes following topical application, and suggested that long-term ocular toxicity in humans was a risk.

In theory, MMC as an alkylating agent will only have an effect on rapidly dividing cells and thus should not affect human corneal endothelium. McDermott *et al.* [47] investigated the effect of MMC at various concentrations (20 – 200 µg/ml) on human corneal endothelium. They suggested that because the human corneal endothelium was essentially an amitotic area, it was not harmed by the exposure. However, they did mention that significant aqueous humor concentrations were reached and the potential for longer-term endothelial toxicity was a possibility.

More studies are needed to establish how much of an effect MMC has on the corneal endothelium and whether there are any associated long-term effects.

2.4 Other uses

As well as the main three uses in ophthalmology already described, topical MMC has been gaining popularity as an adjunctive treatment in corneal and conjunctival squamous cell carcinoma [9,10], ocular cicatricial pemphigoid [48], severe vernal keratoconjunctivitis [11] and dacryocystorhinostomy surgery [49].

When used in the treatment of corneal and conjunctival squamous cell carcinomas, reported side effects have included conjunctival hyperaemia, allergic reaction, punctate keratopathy, punctal stenosis and photophobia, most of which are relatively minor and reversible [9,10,50]. However, a further consideration when MMC is used for neoplastic disorders of the conjunctiva is whether the drug itself causes morphological changes in the conjunctival epithelium, which may be confused with neoplasia.

MMC has been used to treat bladder carcinomas for > 10 years and the changes that it induces in the urothelium are well recognised by pathologists. In particular, pathologists are well aware of the need to differentiate between the effects of topical chemotherapy and recurrent cancer [51,52].

Salomao *et al.* [23] looked at secondary effects of MMC on the conjunctival epithelium and importantly noted that changes did occur, which were very similar to the changes seen in urothelium treated with MMC. An important negative in their findings was that no prominent nucleoli were noted as a chemotherapeutic effect on normal cells. Furthermore, they noted that the changes were seen in the superficial layers as opposed to the deep layers of the conjunctival epithelium, which is an important differentiating factor from recurrent neoplasia.

It is not known how long these changes are likely to remain in the conjunctival epithelium following treatment. Certainly, if changes that occur secondary to MMC in the urothelium are observed, these have been noted to persist for months, and sometimes years, after completion of treatment [51]. The significance of these long-term changes in the eye are unknown at present and need investigation.

3. Contraindications

There are certain conditions in which the use of MMC is not recommended from the outset and could result in significant ocular morbidity. These include patients with dry eyes and neurotrophic disease, because of significant impairment of wound healing in this situation [17], and patients with xeroderma pigmentosa, who have ocular squamous cell carcinoma. In these cases DNA repair is defective and the use of MMC may increase the risk of development of new tumours [53].

There have been reports of MMC causing limbal stem cell deficiency and, hence, the drug should be avoided if there is pre-existing evidence of this [54]. Furthermore, it should be avoided in patients in which the corneal endothelium is already compromised as it has been reported to induce bullous keratopathy in these situations [55].

4. Conclusion

MMC has been widely adopted in ophthalmology and has been shown to be suitable and effective for a wide range of indications. However, significant complications have been reported and, at present, follow-up data in excess of 6 years are lacking in the literature. Of particular concern is its use in refractive surgery in which, often, a young population are treated. In view of its potential side effects, it should be used when no other suitable alternative treatments are available and patients should be fully informed of the risks.

The lowest effective concentration and contact time should be employed in order to limit future complications. In addition, it should be used only by ophthalmologists experienced with its use and who are aware and familiar with the management of associated complications should they arise.

5. Expert opinion

MMC has been shown to be very effective for a number of indications in ophthalmology. The concern is the associated side effects and in particular, the unknown long-term effects given its radiomimetic properties. The questions we should be asking are what alternative treatments do we have and are they as effective?

In pterygium surgery, conjunctival autografting is a well-established technique for primary and recurrent pterygia and has been shown to be very effective in ensuring low recurrence rates [56,57]. Furthermore, there have been trials comparing this technique with those involving MMC, which have shown no significant differences in terms of rate of recurrence [58,59]. As such, it is arguable that MMC should not be used at all in primary pterygia and only used in recurrent pterygia with extreme caution.

In glaucoma surgery, an alternative treatment is 5-fluorouracil, an antifibrotic agent that is not as potent as MMC. Singh *et al.* [60] conducted a randomised clinical trial involving 113 patients comparing 5-fluorouracil with MMC as adjunctive treatment in glaucoma surgery. They concluded that both were equally safe and effective, but the follow-up period was < 1 year. WuDunn *et al.* [61] also showed similar efficacy in their randomised prospective trial and there were no differences in complications encountered. Their follow-up period was also limited to 1 year. However, when we look at high-risk glaucoma surgery, MMC appears to be more effective in intraocular pressure control [62,63]. Ultimately, there is a place for MMC in glaucoma surgery, particularly for those patients at high risk of failure. In any case, these patients are best dealt with by glaucoma experts who are familiar with the management of these often complex patients and who can deal with complications as and when they arise.

In corneal refractive surgery, an alternative treatment in the prevention of haze formation are topical corticosteroids. However, these drugs have not been shown to have significant therapeutic effect in controlled studies [64,65]. MMC, on the other hand, has been shown to have a significant effect, although follow up has been short [42,43]. Of concern is the recently published paper by Morales *et al.* [44] demonstrating statistically significant loss of endothelial cells when MMC was used, although the number of patients enrolled in their study was small (n = 9). Furthermore, the findings do not agree with previously published studies that did not show appreciable damage to the endothelium [42,43].

At present, MMC has a valuable role in refractive surgery, but should be reserved for those patients who are more likely to develop haze formation (i.e., high myopic photorefractive treatments) or as a treatment option in those patients with established haze. It should be used cautiously at the minimum concentration (0.02%) that has been shown to have a therapeutic effect and careful follow up of patients is essential.

In summary, MMC is a useful adjunctive treatment in ophthalmology and has numerous indications. It should be used judiciously with full knowledge of the reported complications, always being aware that there may be effective alternative treatments. Further studies are needed to establish its long-term safety profile.

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