



Review Article

Mitomycin-C Use and Complications in Ophthalmology

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INTRODUCTION

Mitomycin-C, first found its way into ophthalmic use in 1969, in Japan, where recurrent pterygia were successfully treated with the drug which is an antineoplastic / antibiotic agent isolated from the soil bacterium *Streptomyces caespitosus* [1]. It is an anti-metabolite with anti-proliferative effect on cells showing the highest rate of mitosis by inhibiting DNA synthesis and interferes with RNA transcription and protein synthesis [2].

CLINICAL USES

Mitomycin-C should be reconstituted in sterile water at neutral pH, the drug is inactivated in an acidic solution. The drug should be stored under refrigeration to preserve its potency under these conditions, Mitomycin-C is potent for a period of two weeks [3].

DRUG RECONSTITUTION AND PHARMACOKINETICS

The drug is available in a vial (2mg/ml and 10mg/ml). It is further reconstituted with normal saline either 5 ml for 2 mg/ml vial to make 0.4 mg/ml solution or 10 ml for 2 mg/ml vial to make 0.2 mg/ml solution [3]. MMC is delivered in solubilized form. It has high bio-availability in the target tissue because of its hydrophobic character, which favors its penetration into the epithelially denuded cornea and conjunctiva, while deterring its movement into or through intact epithelium [1].

Uses of mitomycin C in ophthalmology

- Ocular surface tumors
- Pterygium surgery
- Glaucoma surgery
- Dacryocystorhinostomy
- Squint surgeries
- Refractive surgeries
- Allergic conjunctivitis and vernal keratoconjunctivitis

Complications

The dosage, the route of delivery/application, the time of exposure and the area of tissue that encounters MMC are important when considering complication rate. Higher MMC concentrations and prolonged exposure times may be associated with a higher risk of complications.

Ocular surface tumours and Pterygium

Ocular surface tumors include a variety of neoplasms originating from the squamous epithelium, melanocytes, and lymphocytic resident cells of the conjunctival stroma. (4) 0.2-0.4 mg/ml applied intra-operatively over bare sclera for 1-5 minutes. Among the most impressive results with ocular surface tumors were double masked, prospective trial using doses of 0.4mg/ml (0.04%) and 1mg/ml four times daily for two weeks [2]. Other reports also describe good results with no serious complications using 0.2mg/ml of Mitomycin-C [5].

Complications

Corneal melting and perforation, corneal edema, seconder glaucoma, scleral calcification. In addition pain, prolonged hyperemia, late hemorrhage, chemosis, lid edema, excessive tearing, ptosis, wound dehiscence, corneal blood staining, photophobia, pigment accumulation, superficial punctate keratitis and delayed wound healing are other rare complications of Mitomycin-C. Periocular allergic contact dermatitis and limbal stem cell deficiency are also important complications of MMC in the treatment of ocular surface tumors [2].

Glaucoma surgery

In filtration surgery of glaucoma, subconjunctival or scleral scarring at bleb cause to high failure rate of trabeculectomy. Mitomycin C use to inhibits the fibroblasts proliferation and subsequent scarring of filtration bleb in filtration surgery. Intraoperative Mitomycin C applied at concentration of 0.2mg/ml controlled post-operative intraocular pressure as effectively as a 0.4mg/ml concentration in high risk cases of congenital glaucoma, but with lower incidence of complications and thin walled blebs [6].

There is no significant difference success or complication between subconjunctival and intra-scleral application of MMC augmented trabeculectomies in glaucomatous eyes at high risk of surgical failure [7].

Administration

Merocel sponge applied in the desired concentration is kept for 1-5 minutes generally subconjunctival and sometimes subsceral (0.2mg/ml or 0.4 mg/ml). After that thoroughly washed with balanced salt solution.

Complications

Cause of late bleb leaks, bleb infections, endophthalmitis, thin walled cystic blebs, corneal epithelial toxicity, corneal or scleral melting, hypotony and hypotonic maculopathy.

Refractive surgeries

After corneal refractive surface surgery. haze formation with loss of corneal transparency, surface irregularities and myopic regression, are the major complications. The use of Mitomycin-C is intended to inhibit wound healing mechanisms leading to sub-epithelial fibrosis. Although some studies suggest that lower concentrations (0.01%, 0.002%) could also be effective in preventing haze when treating low to moderate myopia, Mitomycin-C is usually applied at a concentration of 0.2mg/ml (0.02%) for 12 to 120 seconds over the ablated stroma in laser-assisted *in situ* keratomileusis (LASIK). Single application of diluted MMC 0.02% solution following scraping of the corneal surface was effective and safe in treating haze and regression after photorefractive keratotomy (PRK) for myopia. This dose of MMC has not been associated with any clinically relevant epithelial corneal toxicity [8].

Dacryocystorhinostomy (DCR)

The major cause of DCR failure is fibrosis occurring under the flaps near the osteotomy area. Mitomycin C is used over the anastomosed flaps and osteotomy area to inhibit fibrous proliferation and scar formation. A piece of cotton soaked with 0.2mg/ml MMC is applied to the osteotomy area for 5-30 minutes intra-operatively is safe and effective in maintaining a larger osteotomy size and also improves success rates over the traditional DCR procedure (4.5% vs 11.4%) [9]. A dose ranging from 0.02 to 0.04% applied for a duration of 5 to 30 minutes is effective and no significant complications resulted from its use.

Squint surgeries

The intraoperative application of mitomycin C is a safe and effective adjunct to surgery in the treatment of restrictive strabismus. Topical Mitomycin-C may enhance the success rate of strabismus surgery with delayed adjustment and reduce postoperative adhesions [10]. Mitomycin C when applied intraoperatively helps in reducing postoperative adhesions following strabismus surgery. Dose: 0.2mg/ml for 5 minutes between the conjunctiva and the sclera after adhesion release.

Allergic conjunctivitis and Vernal Keratoconjunctivitis (VKC)

In a study topical Mitomycin-C (0.2mg/ml) was applied four times a day for 3 months and was found to be safe and effective alternative to topical azelastine, in treating allergic conjunctivitis [11]. Topical Mitomycin-C (0.01%) three times daily for a period of two weeks is an effective and safe drug to control acute exacerbations in patients of severe VKC refractory to conventional treatment [12].

General ocular Complications of topical Mitomycin-C

Photophobia, ocular pain, lacrimation, foreign body sensation (secondary to superficial punctate keratitis) and eye lid edema are countable as minor complications of topical Mitomycin-C [3]. Scleral and corneal ulceration and perforation, hypotony, necrotizing scleritis, endophthalmitis, iridocyclitis, cataract, glaucoma and symblepharon are rare and major complications of topical Mitomycin-C [3].

Contraindications of Mitomycin-C for topical use

One-eyed patients, pregnant women, very old patients, severe dry eye, those with predisposing condition to corneal ulceration or poor healing such as immunocompromised patients or patients with Sjogren's syndrome, atopic keratoconjunctivitis, acne rosacea or herpetic keratitis [3].

CONCLUSION

The dose and duration of application of Mitomycin C is still controversial. The use of topical Mitomycin C in ophthalmology is increasing in every subspecialty but risk benefit ratio should be considered, keeping in mind its complications. Further studies are needed to establish the safety and efficacy of this drug.

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