·Review·

Mitomycin C in pterygium treatment

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Received: 2015-04-19 Accepted: 2015-07-02

Abstract

• Pterygium is a benign lesion usually growing from the nasal side of the conjunctiva onto the cornea. Most cases of pterygium does not cause problem or requires specific treatment. The exact cause of pterygium is not clear yet, but some factors are pointed as causes, being the most important the long –term ultraviolet ray exposure. Pterygium surgery is usually considered when there are symptoms that do not respond to conservative treatment. Recurrence is the main complication of the surgery, and much has been done to avoid it. Mitomycin C (MMC) has been used as a fibroblast proliferation inhibitor during the surgery to reduce the chance of recurrence of the pterygium. This review describes the use of MMC as an adjunctive, the optimal dosage, the duration of administration of MMC and possible complications, when used during, after and before the surgery. Most studies suggest that increased exposure (dose or duration) of MMC is associated with a lower recurrence, but with higher risks of complications.

• **KEYWORDS:** mitomycin C; pterygium surgery; recurrence rate
DOI:10.18240/ijo.2016.03.25

Martins TGS, Costa ALFA, Alves MR, Chammas R, Schor P. Mitomycin C in pterygium treatment. *Int J Ophthalmol* 2016;9(3):465-468

INTRODUCTION

The pterygium is classically defined as a degenerative disease of the ocular surface with triangular fibrovascular tissue formation, which grows from the conjunctiva towards the surface of the cornea [1]. Although its pathogenesis has not been fully elucidated, it is very likely that the pterygium represents a degenerative response of the fibrous connective tissue to different stimuli. Among the risk factors, exposure to ultraviolet radiation appears to play an important role in inducing damage to the limbal stem cells. As a result, there is a migration of the conjunctiva towards the cornea, chronic inflammation and fibrovascular tissue formation [2]. Other risk factors described related to the development of pterygium are the micro-traumas in the corneal limbus region and hereditary factors.

The main risk factor is exposure to ultraviolet rays, and a possible explanation of this fact would be the location of pterygium, mainly in the interpalpebral fissure, which is more exposed to sun rays and dust, leading to inflammation of the ocular surface. Recently, it was suggested that there is a mutation in the p53 gene on chromosome 17 as the cause of this disease, and changes in the expression of various growth factors, such as vascular endothelial growth factor A (VEGFA). Histologically, the pterygium is characterized by elastotic degeneration of the conjunctival substantia propria, with eosinophilic and basophilic deposits and fibroblast proliferation[1]. The pterygium is twice as common in men as women[2].

Pterygium was first described in 1000 by AC Susruta, the first ophthalmic surgeon according to the literature [3]. Over the years, many medical treatments have been used, such as bile, urine, acids, radiotherapy, thiotepa, 5-fluorouracil and more recently, mitomycin C (MMC). In the past, the use of horse hair was described to remove pterygium [4]. Surgery is indicated when the patient is feeling discomfort, despite lubricant eye drops, when there is restriction of ocular motility, growth on the visual axis and aesthetic complaints. Currently, conjunctiva transplantation and amniotic membrane transplantation are used. Some surgical techniques consist in excising the pterygium leaving the sclera exposed, but the recurrence rate is up to 88%[5-6]. The purpose of the use of MMC as an adjunctive treatment is to prevent the recurrence of pterygium after the surgery[7].

METHODS

Data collection was made through extensive computer-assisted searches in PubMed for English-language articles and then their references were cross checked. Articles showing recent findings of the use of MMC as an adjunctive treatment of pterygium, optimal dosage, duration of administration and possible complications were included in this review.

Mitomycin C MMC is an alkylating agent which inhibits DNA synthesis. By inhibiting DNA synthesis, it leads to the death of cells caused by the inability to repair the genotoxic injury caused by alkylation. It acts against all cells regardless of the cell cycle and even acts in cells that are not synthesizing DNA. Inhibition of DNA synthesis leads to reduction in the number of mitoses, especially when MMC comes into contact with cells that are in the late G1 and early S phases of the cell cycle. It can be used before, during or after pterygium surgery applied locally or in the form of eye drops. The injection application directly on the pterygium has the advantage of protecting the corneal endothelium and epithelium. Subconjunctival injection allows a more precise dose to be applied to the patient's eye, which usually does not occur with MMC application when using sponges directly on the sclera during surgery. Its action in the prevention of pterygium recurrence occurs by inhibition of fibroblast proliferation in the episclera region. The increased concentration and duration of the application may be associated with complications such as necrotizing scleritis, scleral calcification, ulceration, corneal edema, iritis, glaucoma, cataract, hypotony by injury of the ciliary body and damage to the corneal epithelium and endothelium [8-10].

The administration of MMC in the pterygium surgery is considered off-label by the Food and Drug Administration (FDA), but it is used in cancer treatment.

Mitomycin C During the Surgery Twenty-two trials [11-32] that used MMC application in different concentrations (0.002% to 0.4% for 3 to 5min) applied to the bare sclera after pterygium excision were evaluated. Some studies with primary pterygium determined that all MMC concentrations, from 0.002% to 0.04%, given for 3 to 5min, reduced significantly(P less than 0.0045) the recurrence of pterygium when compared to excision with bare sclera [11,13,15,18].

The recurrence rate reported in the literature for intraoperative use of MMC in primary pterygium surgery varies from 6.7% to 22.5% [32-33]. The most common dose, according to the literature, is 0.02% for 3min in the bare sclera [34]. The surgical technique most used in the studies is the excision of the pterygium with conjunctival autograft transplantation, which has a lower recurrence rate.

In a study, the recurrence rate was 22.5% when MMC was used intraoperatively [11], while other study had a 16.13% recurrence rate.

Complications related to the intraoperative use of MMC vary according to the concentration and the duration of application. With the most commonly used dose, of 0.02% for 2min, there were no severe complications reported[34].

Delayed epithelialization can occur with the use of intraoperative MMC 0.04% for 3 to 5min, but it was not reported with MMC 0.02% for 3min. Iritis and corneal dellen have been reported in 3% of cases when MMC 0.01% was used for 5min intraoperatively [13]. Further studies are needed to determine the optimal concentration of MMC, the exposure time and if it should be applied on the bare sclera, on the Tenon or below the conjunctiva.

Mitomycin C After the Surgery The analysis included 12 trials [16-18,22,25-28,31,35-37] with application of different concentrations of MMC after surgery at different times.

In two studies with MMC application post operatively (0.02% twice a day for 5d) there was reduced primary pterygium recurrence[22,25].

High concentrations of MMC (0.04% 3 to 4 times daily for 7d) result in a significant reduction in the recurrence of pterygium compared to excision with bare sclera[37].

Studies with primary pterygium [23,26] or combined with recurrent pterygium [25,27] reported no significant changes, comparing the use intraoperative or postoperative use of MMC.

Sclera ulceration occurred in a proportion that varied from 5% to 19% in eyes with postoperative MMC 0.02% applied twice daily for 5d[16], with MMC 0.02% applied 4 times daily for 7d[23] and 0.04% applied 3 times daily for 7d[27].

Iritis and corneal dellen occurred with post-operative use of MMC 0.02% four times daily for 7d in 3% of the cases[27].

Two studies[13,17] have shown increased risk of scleral thinning with increasing concentration of MMC application.

Mitomycin C Before the Surgery The pre-operative subconjunctival injection of MMC, in a study of 25 eyes, proved to be efficient, with two cases of delayed epithelialization. Ninety-two percent of eyes with MMC application had no recurrence, 8% had a two week delay in corneal epithelialization. No serious complications were reported[38].

Donnenfeld reported the efficiency and safety of using pre-operative MMC injection of 0.1 mL (0.15 mg/mL) in the pterygium body one month prior to the surgery for pterygium recurrence. The results showed less vascularization and inflammation within the pterygium one month after injection of MMC with a 6% recurrence after 2y of follow up[39].

The risk of preoperative injection is due to the impossibility of washing the MMC that is in the subconjunctival space and can generate toxicity. Studies showed that subconjunctival injection of MMC 0.2 mL (0.4 mg/mL) injected 2 mm posterior to the limbus caused cell changes, such as flattening and pyknotic nuclei in the ciliary body epithelium, leading to reduction of aqueous humor production a month after the injection[40].

Carrasco *et al* [41] reported a case of scleral necrosis in a patient who received a subconjunctival injection of MMC 0.15 mg/dL one month before pterygium surgery, but it was a patient with a severe dry eye history.

The subconjunctival injection does not allow the tear to dilute the MMC, which increases the exposure time.

In conclusion, the data from the studies show that the use of MMC, along with the conjunctival autograft technique, reduces even more the recurrence of pterygium, and the use of MMC alone does not reduce recurrence as much as when the adequate surgical technique is used along with MMC[42].

Intraoperative and postoperative use of MMC with conjunctival transplantation demonstrated low recurrence rate and good cosmetic results in the treatment of pterygium.

The preoperative injection of MMC with a low dose before surgery showed good results in preventing the recurrence of pterygium.

Most studies suggest that increased exposure (dose or duration) of MMC is associated with a lower recurrence, but with higher risks of complications. Thus, there is a need for new long-term studies to determine the optimal dosage and duration of administration of MMC, since many complications described in literature occur years after the procedure.

ACKNOWLEDGEMENTS

Conflicts of Interest: Martins TGS, None; **Costa ALFA,** None; **Alves MR,** None; **Chammas R,** None; **Schor P,** None.

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