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The efficacy of using intraoperative compared with postoperative topical 0.04% Mitomycin-C drops to the recurrence of Pterygium

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ABSTRACT

Suhardjo - ***The efficacy of using intraoperative compared with postoperative topical 0.04% Mitomycin - C drops to the recurrence of pterygium***

Background: The major problem in the treatment of pterygium is to prevent recurrences after surgical excision. To prevent the neovascularization and recurrence, variable doses and administration of mitomycin C installation had been used. However no single treatment has been universally effective yet.
Objective: The purpose of this studies is to evaluate the safety and efficacy of two different methods of 0.04% Mitomycin – C application as adjunctive chemotherapy to the recurrence of pterygium.
Methods: The research had been conducted at the Dr. Sardjito Central Hospital, Wates Central Hospital Gombong PKU Hospital, and Purworejo Aisyiah Hospital from January 1995 to December 1998. Eighty eight patients underwent pterygium excision were involved in this study, and divided into two groups. Group I or intraoperative 0.04% MMC group of 44 cases receiving 0.04% MMC drops applied to the bare sclera for 4 minutes intraoperatively. Group II or post operative group of 44 cases receiving 0.04% MMC eye drops one day after excision once daily during the first postoperatively week and continued with a dosage of one drop 3 times a day during the second postoperative week. Observations were done daily during the first postoperative week, weekly during the first postoperative month, and monthly up to 6 months. Observations were done including of the symptoms of recurrence and side effects of the treatment. The data were analyzed using the Student's test and chi square technique.
Results: In the intraoperative group, 6 cases (13.67%) recurred, 2 cases of superficial punctate keratitis. In the postoperative group, 7 cases (15.95%), and 3 cases superficial punctate keratitis. There was no statistical difference in the rates of recurrence (x^2 = 0,0902, p>0,05). Most of the cases of pain, tearing and lid edema occurred in the group intra-operative. No other complication was observed in the course of the study.
Conclussion: A single dose intraoperative application of MMC is a simple, economic, affective alternative adjunctive treatment for pterygium.

Key words : Intraoperative mitomycin-C – pterygium excision – recurrence

ABSTRAK

Suhardjo - ***Daya guna penggunaan mitomisin C 0,04% tetes mata intra-operasi dibanding pascaoperasi terhadap kekambuhan pterigium***

Latar Belakang penelitian: Masalah utama pada pengobatan pterigium adalah mencegah kekambuhan pasca pembedahan. Terdapat beberapa cara maupun berbagai dosis pemberian mitomycin – C untuk mencegah timbulnya neovaskularisasi dan kekambuhan pterigium, namun demikian belum ditemukan satu cara pengobatan yang seragam.
Tujuan penelitian: Penelitian ini bertujuan untuk mengevaluasi daya guna dua cara penggunaan mitomycin-C 0,04% sebagai kemoterapi tambahan terhadap kekambuhan pterigium.
Bahan dan cara penelitian: Penelitian dilakukan di RSUP. Dr. Sardjito, RSU. Wates, RS. PKU. Gombong, RS. Aisyiah Purworejo, antara bulan Januari 1995 sampai Desember 1998. Dilakukan eksisi pterigium pada 88 pasien, dan dibagi dua kelompok menjadi kelompok I dan II. Kelompok I mendapat mitomycin-C durante pembedahan sebanyak 44 pasien. Kelompok II dengan jumlah yang sama, diberikan mitomycin-C tetes mata 0,04% sehari pasca operasi sebanyak satu kali sampai 1 minggu dan dilanjutkan 3 kali sehari sampai 2 minggu. Pengamatan dilakukan tiap hari selama 1 minggu, seminggu sekali sampai satu bulan, dan sebulan sekali sampai 6 bulan. Diamati tanda-tanda kekambuhan dan efek samping pengobatan. Terhadap data-data yang didapat dilakukan analisis statistik dengan uji t Student dan chi kuadrat.

Hasil: Angka kekambuhan pada kelompok intra operasi sebanyak 13,67% (6 kasus), dan kelompok pasca operasi sebesar 15,91% (7 kasus). Berdasarkan analisis statistik, ternayata tidak dijumpai perbedaan yang bermakna (x^2 = 0,0902, p >0,05). Efek samping pengobatan berupa keratitis superfisial pungtata, dijumpai 2 kasus pada kelompok intra-operasi dan 3 kasus pada kelompok pasca operasi. Efek samping lainnya berupa rasa sakit, lakrimasi, dan sembab kelopak mata lebih sering dijumpai pada kelompok intra-operasi.
Simpulan: Penggunaan mitomycin-C intra-operasi sangat sederhana, dan efektif sebagai terapi tambahan alternatif pada pterigium.

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INTRODUCTION

Pterygium constitutes the third most common eye disease in Indonesia. The result of surgery for pterygium are reasonably good, but recurrences are frequent, ranging from 0-69,44%[1,2]. Repeated surgical procedures often worsen the situation, as loss of the conjungtival tissue and scarring can result in obliteration of the fornices. To prevent the neovascularization and recurrence, many researchers used Strontium 90, thiotepa solution and mitomycin - C (MMC) as adjunctive in the treatment of pterygium.

Mitomycin - C is an antibiotic- anti neoplastic agent isolated from Streptomyces calspitasus, that may inhibit the synthesis of cellular DNA, RNA and protein. Variable dose of MMC instillation has been used. Mori *et al* reported the MMC instillation three times daily for 2 weeks and the recurrence rate of 13%[3], but severe scleral damage and scleromalacia were reported as complication of pterygium excision and using post operative MMC[4,5]. The use of postoperative topical MMC drops by some ophthalmologist in Yogyakarta still occurred. On the other hand, intra-operative MMC as adjunct chemotherapy with pterygium excision had shown good result[6,7] . The problem of the study is : which one among those methods has lower recurrence rate and more safety.

The purpose of this studie is to evaluate safety and efficacy of two different regimens of MMC application as adjunctive chemotherapy to the recurrence of pterygium. These knowledge will render a more appropriate treatment, a better cure rate, and less complication.

MATERIALS AND METHODS

Patients with pterygium attending the ophthalmic outpatient clinic of Dr Sardjito Central Hospital, Wates General Hospital, Gombong PKU Hospital, and Purworedjo Aisyiah Hospital from January 1995 to December 1998 were included in the present study. The pterygium of 88 patients were surgically excised using a bare sclera technique. The patients were divided into two groups, 44 cases (group I) receiving 0.04 % MMC drops applied to the bare sclera for 4 minutes intra operatively, the other group, 44 cases (group II) receiving post operative 0.04 % MMC drops once daily one drop in the first week and 3 times daily one drop in second week.

Patients who had recurrent pterygium, conjunctivitis, keratitis, uveitis, dry eye and scleritis were excluded from the study. A medical assessment was performed in each case before surgery. Patients who exhibited postcompliance or who were lost to follow up were excluded from the study population.

The surgical technique was the same in all cases. Corneal and conjunctival anesthesia was achieved with topical 0,5% pentocain, and 0,3-0,4 ml of 2% lidocaine was injected subconjunctivally in the body of the pterygium with 27 gauge needle. Pterygium excision was performed with keratome, starting from the apex and dissecting to the scleral extension, having the bare sclera expose. The apex of the pterygium was held with one forcep and pulled of the sclera by pulling it toward the body. A blade was then used to polish and smooth the corneal surface and clean anytime remnant still adherent to the cornea. Cauterization was used during the surgery. Conjunctiva have a bare sclera. Th use of topical steroid-antibiotic ointment was followed by an eye patch for one day.

For the patients group I receiving intraoperative MMC, a sponge soaked with 4 drops 0.04% MMC was put on the bare sclera, were dropped over it for 4 minutes. Steroid-antibiotic ointment were used postoperatively for one week, and continued with 3 times daily steroid-antibiotic drops

in the second week. The patients group II receiving 0.04% MMC. One drop once every day together with topical steroid-antibiotic eye ointment in the first week, and 3 times one drop together steroid-antibiotic drops in the second week. Observation was done daily for one week, weekly for one month, and monthly up to 6 month. At each visit, a full ophthalmologic examination was performed and any ocular tissue changes was observed. Recurrences was defined as any conjunctival tissue starting to pass the limbus.

The results are expressed as mean, and frequency. The data were analyzed using the Student's t test and chi square. The minimum level of significance was considered as $p < 0.05$.

RESULTS

The patients age range between 27-72 years in group I, and 17-60 years in group II. Each group consisting of 29 females and 15 males, and group II consisting of 27 females and 17 males. All patients live in rural territories, and almost all patients work as farmer with daily sunlight exposure.

The mean age of group I was 35.69 ± 4.70 years and 52.93 ± 8.84 years. In the group II, the mean age was 31.05 ± 6.10 years and 50.86 ± 6.55 years. Statistically, there were no difference in age and sex between group I and group II (TABLE 1).

Indonesia is a tropical areas which encircles the earth that extends from 37 degrees north to 37 degrees south of the equator. Pterygium in Indonesia is considered to be the manifestation of chronic irritation by solar radiation, repeated micro trauma and abnormality of tear film. Many patients who had thick vascular pterygia (inflammed type) and the other patients had thin membranous pterygia. More than one half patients were 40 years old and more had thin membranous pterygia.

By chi square test analysis, there was no difference in recurrence rate between the young group (< 40 years old) and the old group (≥ 40 years old) in both groups (TABLE 2). All pterygiam that recurred (16 cases) during the follow-up period were retreated with excision and than received postoperative MMC drops four times daily for 2 weeks.

Neovascularization, granulations and recurrence occurred in 6 patients (13.67%) in group I and 7 patients (15.91%) in group II. However, these differences were not statistically significant ($x^2 = 0.0902$, $p > 0.05$). No recurrence found in patients of more than 50 years old. All pterygia that recurred (11 cases) during the follow up period were retreated with excision and then received intra-operative and postoperative MMC 0.04% for 2 weeks.

The postoperative complications were relatively comparable between two groups (TABLE 3). In the patients treated intraoperatively, there were 2 cases of superficial punctate keratitis, 3

TABLE 1. – Demographic data all patients

Data	Group I	Group II	Statistical analysis
Age	28-72 Years	17-60 Years	
mean age (< 40 years)	35.69 ± 4.70	31.05 ± 6.10 years	t = 0.18 *
mean age (≥ 40 years)	52.93 ± 8.84	50.86 ± 6.55 years	t = 0.021 *
Sex			
male	15	17	
female	29	27	$x^2 = 0.30$ *

x) $p > 0.05$

TABLE 2. – Age group and recurrence rate after 6 months follow up

Group	Number of cases	Recurrent Cases	Recurrent rate	Statistical analysis
I (Intraoperative)				
< 40 years old	14	3	21.43%	
≥ 40 years old	30	3	10%	$x^2 = 1.055$ *
II (Postoperative)				
< 40 years old	21	2	9.53%	
≥ 40 years	23	5	21.74%	$x^2 = 1.223$ *

x) $p > 0.05$

cases of pain, 3 cases of tearing and 2 cases of lid edema. In the patients group II, only 3 cases of superficial punctate keratitis occurred.

TABLE 3. – Side effects of using MMC 0.04%

Side effects	Group I	Group II
Superficial punctate Keratitis	2	3
Pain	3	0
Tearing	3	0
Lid edema	2	0

Side effects occurred in group I were pain, tearing, lid edema. Infection, ulceration, uveitis, glaucoma and necrosis of the sclera did not occur. Slight photophobia which disappeared after 7 days after application in almost all patients. No systemic complications were experienced.

DISCUSSION

Pterygium is a degenerative corneal limbal process characterized by exuberant fibrous tissue proliferation of unknown etiology. It is a common condition in Indonesia. Hot, wet and dry climates and ultra violet radiation have been implicated as major predisposing factors in primary pterygium occurrence. Pterygium is composed in part of newly by synthezid elastic fibers that is presumably elaborated by actinically damaged fibroblasts of the substantia propria[3].

In the literature, different rates of recurrence were reported by many authors. Rabie[2] reported that the recurrence rate of laser surgery for pterygium was 0%, but Mokbe[1] 17.78 - 69.44%. Many research workers reported various doses of MMC to reduce the recurrence rate. Siti Tjahjono[6] using 0.1 mg/ml MMC intraoperatively as adjunct chemotherapy with pterygium excision found 10.7% recurrence rate. Helal *et al*[7] using the same concentration found 5.57% recurrence rate. Many modulation of adjunctive treatments with variable success rates have been developed, but no single treatment has been universally effective[9,10]. An important principle in the prevention of recurrence is to stop the new vessel formation in the bared episclera surface. Rapid epithelialization also helps on diminish the formation of granulation tissue. MMC inhibits DNA synthesis, this preventing cell division and diminishing cell viability. Its greatest antiproliferative effect is on the cells that show the highest rate of mitosis. MMC usage with pterygium excision retards the regrowth of granulation tissue by its antiproliferative effect. There was no statistical difference in the rates of recurrence or postoperative complications between the two groups. The intraoperative application of MMC has the advantages of not being influenced by patient compliance, requiring fewer post operative medications, and a lesser chance of developing a cumulative dose of MMC.

Singh *et al*[11] reported ocular pain, photophobia, tearing, and foreign body sensation in the first to second week postoperative. They were marked when they used a 1 mg/ml concentration rather than 0.4 mg/ml concentration of MMC drops. Some of these symptoms remained as long as 6 to 8 weeks postoperative in some patients especially in inflammed type.

Rubienfield et al[12] described a series of ten patients who experienced serious vision – threatening complications associated with the use of MMC after pterygium surgery. These included severe glaucoma, corneal edema, corneal perforation, corectopia, iritis, sudden onset of mature cataract, scleral calcification, incapacitating photophobia, and pain. The MMC concentration, the surgical technique, the use of too much cautery or the presence of underlying ocular or systemic disease may contribute to such complications. In this studies, the ocular complications were minor and easily managed medically.

Surgical excision using the bare sclera technique is simple, requires no special skill or experiences and has less conjunctival manipulation compared to the conjunctival autograft technique. Cauterization is done during surgery, to avoid neovascularization and granulations. The use of single dose 0,04% MMC is economic and safe to avoid adverse reactions of MMC.

Both methods of MMC application with simple surgical excision were found to be safe and effective in minimizing pterygium recurrence. The single, intraoperative application of MMC would seem to be a useful and effective alternative therapeutic option in the treatment of pterygia. This treatment modality should be investigated further to determine its optimal dose and exposure time as well as its long-term safety.

CONCLUSION

Forty four patients with pterygium underwent bare sclera technique and received 0.04% MMC topical intraoperative, 13.67% recurred. The other group of 44 patients who received 0.04% MMC topical post-operative, 15.91% recurred. However, these difference were not statistically significant ($x^2 = 0.0902, p > 0.05$).

Among the intra-operative group, there were 3 patients with pain and tearing, 2 patients with lid edema as adverse reactions, and none was found in the postoperative group. Superficial punctate keratitis was found higher in the postoperative group. No serious ocular and systemic complications in either group. A single dose intraoperative application of MMC is a simple, economic, effective alternative therapeutic option in the treatment of pterygium. To date, there has been no evidence of scleral complication and visual loss. Because this study was relatively short, further studies is needed to determine the long-term results.

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