Original Article/นิพนธ์ต้นฉบับ

ผลของ Mitomicin C (MMC) ต่อเซลล์กระจกตาด้านในภายหลังการผ่าตัดต้อเนื้อ

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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาผลของยา Mitomycin C (MMC) ต่อเซลล์กระจกตาด้านในและอุบัติการณ์การกลับเป็นซ้ำ ในผู้ป่วยที่เข้ารับการผ่าตัดต้อเนื้อในโรงพยาบาลรามาธิบดี

วิธีการวิจัย: การวิจัยแบบ prospective randomized study

วิธีการ: เป็นการศึกษาในผู้ป่วยที่เข้ารับการผ่าตัดต้อเนื้อที่โรงพยาบาลรามาธิบดีในช่วง เมษายน - กันยายน 2552 โดยแบ่งผู้ป่วยเป็น 2 กลุ่ม กลุ่มแรก วาง MMC นาน 30 วินาทีก่อนวาง conjunctival graft กลุ่มที่ 2 เป็นกลุ่มควบคุม ไม่วาง MMC โดยได้รับยาหลังผ่าตัด ชนิดเดียวกัน ก่อนการผ่าตัดผู้ป่วยทั้ง 2 กลุ่มได้รับการตรวจตาอย่างละเอียดและวัดขนาด (Polymegethism) รูปร่าง (Pleomorphism) และจำนวน (Endothelial cell density) ของเซลล์กระจกตาด้านใน จากนั้นผู้ป่วยได้รับการตรวจวัดการมองเห็น ความดันลูกตา การกลับเป็นซ้ำและวัดขนาด รูปร่างและจำนวนของเซลล์กระจกตาด้านในซ้ำ ที่ 1 และ 3 เดือน นำค่าขนาด รูปร่างและจำนวนของเซลล์กระจกตา รวมถึงอุบัติการณ์กลับเป็นซ้ำมาเปรียบเทียบกันทางสถิติ

ผลการศึกษา: จากผู้ป่วยที่เข้ารับการผ่าตัด 18 ราย อายุระหว่าง 33-75 ปี (เฉลี่ย 56.56+/-9.81ปี) ได้รับการวาง MMC 9 ราย ไม่วาง MMC 9 ราย เมื่อเปรียบเทียบทางสถิติพบว่าค่าเฉลี่ยขนาด รูปร่างและจำนวนเซลล์กระจกตาก่อนผ่าตัด หลังผ่าตัด 1 และ 3 เดือน ของทั้ง 2 กลุ่มไม่แตกต่างกันทางสถิติ (Polymegethism; P = 0.587, 0.258, 0.116, Pleomorphism; P = 0.566, 0.217, 0.345, Endothelial cell density; P = 0.366, 0.950, 0.703 ตามลำดับ) จากระยะเวลาติดตามผลเฉลี่ย 6.67+/-1.57 เดือนพบการกลับเป็นซ้ำ 2 รายในกลุ่มควบคุม (22.22%) ไม่พบภาวะแทรกซ้อนที่รุนแรงจากการผ่าตัด

สรุป: การวาง MMC ในการผ่าตัดต้อเนื้อไม่มีผลต่อการเปลี่ยนแปลงขนาด รูปร่าง และจำนวนของเซลล์กระจกตาด้านในและอุบัติการณ์การเป็นซ้ำอย่างมีนัยสำคัญทางสถิติ **จักษุเวชสาร 2553; กรกฎาคม-ธันวาคม 24(2): 79-85.**

ภาควิชาจักษุวิทยา คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี

Original Article/นิพนธ์ต้นฉบับ

Effect of Mitomycin C on Corneal Endothelium in Pterygium Excision

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Abstract

Objective: To compare the change of corneal endothelium in patients undergoing pterygium excision with conjunctival autograft and with or without adjunctive mitomycin C (MMC).

Design: Prospective randomized study.

Methods: A prospective study in pterygium patients who were operated with or without MMC in Ramathibodi hospital during April 2009 - September 2009. Patients' age, gender, corneal endothelial cell density, polymegethism, and pleomorphism at preoperative period, 1 month, and 3 months post operation were recorded. The results were analysed by paired t-test. Recurrence and complication were observed until January 2010. Recurrence was analysed by Fisher's exact test.

Results: There were 18 eyes of 18 patients included in this study, 9 eyes were operated with adjunctive MMC and 9 eyes without MMC. There were no statistical significance in corneal endothelial cell density (P = 0.366, 0.950, and 0.703 respectively), polymegethism (P = 0.587, 0.258, and 0.116 respectively) and pleomorphism (P = 0.566, 0.217, and 0.345 respectively) of preoperative period, 1 month and 3 months post operation in the two groups. Recurrences were found in 2 eyes (22.22%) of control group at the 3rd month (P=0.470, Fisher's exact test). No serious complication was found in either group.

Conclusions: Effects on corneal endothelium in pterygium excision and conjunctival autograft with or without MMC did not differ significantly. There was no statistical significance in recurrence rate between MMC and control groups. **Thai J Ophthalmol 2010; July-December 24(2): 79-85.**

Keywords: Pterygium excision, Conjunctival autograft, Corneal endothelial cell density, Polymegethism, Pleomorphism, Mitomycin C.

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Introduction

Pterygium, an external eye disease, is common worldwide but is particularly prevalent in tropical and subtropical areas. The prevalence rates range from 0.7 to 31% among different populations[1-6] and are also influenced by age, race and exposure to solar radiation.

Various surgical techniques have been described in the literature in treating pterygium, which includes bare sclera techniques, beta irradiation, intra and post operative mitomycin, conjunctival autograft , amniotic membrane transplant and some combination of the above mentioned procedures. However, the most common problem in all these procedures is recurrence.

Mitomycin C is an antimetabolite agent produced by a strain of *Streptomyces caespinosus.* It inhibits synthesis of DNA, RNA and proteins. Recently, many studies have reported the efficacy of mitomycin C in minimising recurrences of surgically excised pterygia when used as an adjunctive therapy.

Sagev, et al. described the combined mitomycin C application and free flap conjunctival autograft technique in 2003. They reported the recurrence rate of pterygium can be markedly reduced. There were no sight-threatening complications or serious side effects.[7]

The method of use and the dosage is not yet standardized but different reports indicate dosages ranging from 0.2 to 1 mg/ml.[8-12] Some investigators have used mitomycin C in the dosage of 0.2 to 0.4 mg/ml and a follow-up for three years has shown a recurrence rate of 6.6 to 13%.[8,12]

Frucht-Pery reported that pterygium excision with a free conjunctival autograft combined with intraoperative low-dose MMC (one minute application of MMC, 0.2 mg/ml) is a safe and effective technique in pterygium surgery.[13]

Nevertheless, Avisar, et al. reported an immediate and significant effect on endothelial cell density (endothelial cell loss) of 5-minute application of MMC 0.02% to the bare sclera during pterygium surgery.[14]

There are no published data on the results of the Thai experience with excision combining mitomycin C application and conjunctival autograft technique. Indeed, being geographically located in the tropical area and exposed to solar radiation, less than optimal results might be expected. We performed the current study in order to evaluate the effect of MMC on corneal endothelium and recurrence rates with this technique in Thailand.

Material and Methods

A prospective study in pterygium patients who were operated with or without MMC by block randomization in Ramathibodi hospital during April - September 2009.

The patients with primary and recurrent pterygium were included. Patients with pseudopterygium, history of ocular diseases predisposing to ulceration or poor wound healing such as autoimmune disease, collagen vascular disease, dry eye, ocular trauma and glaucoma were not included in the study.

18 eyes of 18 patients were included in the study. There were 4 male and 14 female patients. Age range was 33 to 75 years. All patients underwent total ophthalmic examination. Preoperative data sheet included name, age, sex, BCVA, type, extent and location of pterygium, corneal endothelial cell density, polymegethism (coefficient of variation) and pleomorphism (percentage of hexagonal cells) (by Specular Microscope EM-3000; Tomey Corporation, Nagoya, Japan).

Written informed consent was obtained from each patient.

The patients were divided into two groups. The

MMC group (n=9) underwent pterygium excision followed by application of 0.2 mg (0.02%) MMC for 30 seconds along with conjunctival autograft. The control group (n=9) underwent pterygium excision with conjunctival autograft without MMC.

All eyes were given topical anesthesia. The surgical procedure was as follows:

After cleaning the eye with Betadine paint, eyelids were retracted by a self retaining eyelid retractor. Local anesthesia was given intralesionally. The head of the pterygium was separated from the cornea and 4-5 mm conjunctiva including the body of the pterygium was excised. Light cautery was applied to bleeding points for hemostasis. A sterile sponge (2x3 mm) soaked in freshly prepared 0.02% of MMC was applied over the resected pterygium site of the MMC group for 30 seconds. The sponge was removed after 30 seconds and the eye was irrigated with balanced salt solution.

Conjunctival autograft was collected from the ipsilateral superior limbic area and sutured with 10-0 Nylon on to the bare sclera of both groups. At the end of surgery, eyes of all patients were patched after applying 3%chloramphenical eye ointment. Patients were asked to return on the first post-operative day and the eye dressings were opened.

Post-operative medicine regimen was same in both groups, consisting of topical antibiotic plus steroids drops (Dex-oph®) four times a day and ointments (Maxitrol®) once daily for 1 month after operation.

All patients were followed up on the first post-operative day, then 2 weeks (stitch off), 1 month, 3 months and then 6 months apart.

Follow-up examination included visual acuity assessment, intraocular pressure and slit lamp examination. Corneal endothelial cell density, polymegethism and pleomorphism was obtained at 1 and 3 months postoperatively by the same technician (Specular Microscope EM-3000; Tomey Corporation, Nagoya, Japan). Outcome was assessed on the basis of corneal endothelial cell density, polymegethism, pleomorphism, any pterygium recurrence, time of recurrence and any post operative complication.

An encroachment of 1 mm or more clear cornea from the limbus by fibrovascular proliferative tissue in the site of previous pterygium surgery was considered as recurrence.

The main outcome is mean corneal endothelial cell density, polymegethism and pleomorphism. It was analysed by paired t-test. Recurrence and complication were observed until January 2010. Recurrence was analysed by Fisher's exact test.

Results

There were 18 eyes of 18 patients in this study (14 females and 4 males; age range of 33-75 years, mean 56.56 +/- 9.81years; 17 primary cases and 1 recurrence case). 9 eyes were operated with adjunctive MMC 0.02% and 9 eyes without MMC. Mean corneal endothelial cell density of each group was recorded preoperatively, 1 month, and 3 months postoperatively as shown in table 1. There was no statistical significance in corneal endothelial cell density of preoperative period, 1 month, and 3 months post operation in the two groups (P = 0.366, 0.950, and 0.703 respectively, paired t-test).The other parameters (i.e. polymegethism and pleomorphism) were recorded as shown in table 2 and 3. There was no statistical significance in polymegethism (P = 0.587, 0.258, and 0.116 respectively, paired t-test) and pleomorphism(P = 0.566, 0.217, and 0.345 respectively, paired t-test) of preoperative period, 1 month, and 3 months post operation in the two groups.

Table 1 Mean corneal endothelial cell density of preoperative, 1 month and 3 months post operation

	Mean corneal endothelial cell density (cell/mm^2)		p-value*
	MMC group	Control group	
Preoperative	2528+/-249.05	2413.33+/-290.16	0.366
1 month	2489.89+/-242.43	2482.56+/-232.02	0.950
3 months	2521.67+/- 286.75	2482.33+/-243.68	0.703

(*paired t-test, P<0.05)

Table 2 Mean polymegethism (coefficient of variation) of preoperative, 1 month and 3 months post operation

	Mean coefficient of variation		p-value*
	MMC group	Control group	
Preoperative	0.41+/-0.07	0.39+/-0.07	0.587
1 month	0.40+/-0.03	0.38+/-0.04	0.258
3 months	0.39+/-0.02	0.37+/-0.03	0.116

(*paired t-test, P<0.05)

Table 3 Mean pleomorphism (Percentage of hexagonal cells) of preoperative, 1 month and 3 months post operation

	Mean Percentage of hexagonal cells (%)		p-value*
	MMC group	Control group	
Preoperative	36.22+/-11.45	39.89+/-9.40	0.566
1 month	35.78+/-9.11	41.00+/-6.10	0.217
3 months	37.00+/-6.95	39.22+/-3.46	0.345

(*paired t-test, P<0.05)

The follow- up period was from 5 to 10 months, mean was 6.67 +/- 1.57 months. The corneal endothelial cell density was recorded and analysed at 0, 1 and 3 months. Recurrence was observed during the follow-up period.

Recurrences were found in 2 eyes (22.22%) of control group at the 3rd month (P=0.470, Fisher's exact test). No serious complication was found in either group.

Discussion

Pterygium is a common ocular surface disorder in Thailand. Combined mitomycin C application and conjunctival autograft is one of various surgical techniques used in treating pterygium. There are literature reports that the recurrence rate of pterygium can be markedly reduced with no sight-threatening complications or serious side effects.[15] Nevertheless, the use of mitomycin C leads to complications such

as scleromalacia, scleral ulcer and cataract, as has been described after pterygium excision. Other less common complications are necrotizing scleritis, perforation, iridocyclitis, glaucoma, scleral calcification[8,9,11,12] and lower lacrimal punctal occlusion.[9]

There are literature reports of the significant effect of mitomycin C on endothelial cell density[15,16] while some have shown no significant effect.[17] The effect is significant endothelial cell loss. Timing and dosing of mitomycin C application are different among these studies, ranging from 1 to 5 minutes of 0.2-0.4 mg/ml MMC application.

We reported the comparison of the change of corneal endothelium in patients undergoing pterygium excision with conjunctival autograft with and without adjunctive mitomycin C (MMC). We used the same techniques by 3 surgeons to harvest and suture conjunctival autograft. The MMC group underwent pterygium excision followed by application of 0.2 mg (0.02%) MMC for 30 seconds along with conjunctival autograft. To minimize the potential side effects of mitomycin C, we sought to use the lowest concentration and application time possible of mitomycin C and avoided application to the conjunctival and corneal epithelium.

There was no statistical significance in corneal endothelial cell density, polymegethism and pleomorphism of preoperative period, 1 month and 3 months post operation in both groups. Recurrence was found in the control group but showed no statistical significance. Our limitations are small sample size and short follow up period.

No serious complication was found in either group but we have no data for long term complication.

However, we believe that this treatment should be avoided in patients with wound-healing abnormalities or dry eye syndrome because of the increased risk of mitomycin C-associated complications.[18]

Mitomycin C is a radiomimetic agent with the potential to cause long-term complications; therefore, additional long-term studies are necessary to establish the safety and efficacy of mitomycin C as adjunctive therapy for pterygium excision.

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