Conjunctival Autografting Combined With Low-Dose Mitomycin C for Prevention of Primary Pterygium Recurrence

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• PURPOSE: To compare the clinical outcome of pterygium surgery combining intraoperative mitomycin C (MMC) with a free conjunctival autograft, with three other methods of pterygium surgery, including intraoperative MMC alone, conjunctival autograft alone, and bare sclera without adjunctive treatment.

• DESIGN: Interventional, randomized and in part non-randomized, prospective, comparative study.

• METHODS: SETTING: A university medical center department of ophthalmology. STUDY POPULATION: One hundred and twenty patients underwent pterygium excision surgery. These patients were divided into four treatment groups. INTERVENTION: In group 1 (30 patients), MMC, 0.2 mg/ml, was applied for three minutes. In group 2 (30 patients), conjunctival autografting was performed. Group 3 (30 patients) received sodium chloride 0.9% only, and group 4 (30 patients) underwent conjunctival autografting combined with one minute application of MMC, 0.2 mg/ml. MAIN OUTCOME MEASURE: Recurrence rates and complications.

• RESULTS: Pterygium recurred in two patients (6.6%) in group 1, in four patients (13.3%) in group 2, in 14 patients (46.6%) in group 3, and in none of the patients in group 4. χ² analysis revealed a significantly lower recurrence rate in group 4 compared with group 2 (P = .038) and with group 3 (P < .0001). Epithelialization of the wounds was complete within 14 days of surgery. No complications were demonstrated in any of the study groups except for one case of minor melting of the flap in group 4.

• CONCLUSIONS: This study indicates that pterygium excision with a free conjunctival autograft combined with intraoperative low-dose MMC is a safe and effective technique in pterygium surgery. (Am J Ophthalmol 2006;141:1044–1050. © 2006 by Elsevier Inc. All rights reserved.)

MITOMYCIN C (MMC) IS AN ANTIBIOTIC-ANTINEOPLASTIC AGENT THAT SELECTIVELY INHIBITS THE SYNTHESIS OF DNA, CELLULAR RNA, AND PROTEIN.1,2 IN THE LAST DECADE, A SINGLE INTRAOPERATIVE DOSE OF MITOMYCIN C HAS BEEN USED IN GLAUCOMA FILTERING PROCEDURES AND IN PTERYGIUM SURGERY. IN FILTERING PROCEDURES FOR GLAUCOMA PATIENTS, THE RATE OF BLEB FAILURES HAS DECREASED AND THE SURGICAL OUTCOME OF PREVIOUSLY FAILED FILTERS HAS IMPROVED.3–4 NO OCULAR SURFACE–RELATED COMPLICATIONS OF MMC IN FILTERING PROCEDURES HAVE BEEN REPORTED.

MMC HAS ALSO BEEN USED IN PTERYGIUM SURGERY. POSTOPERATIVE ADMINISTRATION OF TOPICAL MITOMYCIN 0.02% (0.2 mg/ml) TO 0.1% (1 mg/ml) DROPS DECREASED THE RECURRENT RATE OF PTERYGIUM TO A RANGE OF 2% TO 11%.5–8 HOWEVER, POSTOPERATIVE COMPLICATIONS WERE REPORTED EVEN WHEN A LOW DOSAGE OF MITOMYCIN WAS APPLIED.8,9 THE MAJOR REASONS FOR COMPLICATIONS WERE RELATED TO UNCONTROLLED AND PROLONGED USE OF THE DRUG BY THE PATIENTS.8,9 A SINGLE INTRAOPERATIVE APPLICATION OF TOPICAL MITOMYCIN C DURING THE EXCISION OF PTERYGIUM HAS DECREASED THE RECURRENT RATE OF PTERYGIUM AS WELL AS THE RATE OF COMPLICATIONS.10–12

Conjunctival autotransplantation is a common procedure for primary and recurrent pterygium, with recurrence rates ranging from 2% to 39%.13–18 Conjunctival autotransplantation combined with adjunctive MMC for primary and recurrent pterygium was reported in two previous studies, with a recurrence rate of 2% to 9%.17,19,20 These reports, however, did not compare the outcome with other surgical techniques.

In the present study, we report our experience with conjunctival autotransplantation combined with intraoperative application of MMC for primary pterygium and compare it with other techniques of pterygium excision, including MMC alone, conjunctival autograft alone, or leaving a bare sclera with no adjunctive treatment.

METHODS

THE STUDY ADHERED TO THE TENETS OF THE HELSINKI DECLARATION. INFORMED CONSENT WAS OBTAINED FROM EACH
patient following a detailed explanation of all of the surgical procedures. One hundred and twenty patients with primary pterygia were recruited to this study and underwent pterygium surgery using one of four methods. Sixty consecutive patients who had primary pterygia underwent excision of pterygium between July 1996 and June 1997. These 60 patients were randomized into two treatment groups of 30 patients each (Table 1). The surgeon and the examiners were not masked to the treatment during the surgery. Upon completion of pterygium removal, patients in group 1 received a single intraoperative dose of MMC 0.02% (0.2 mg/ml) for three minutes, whereas in group 2 free conjunctival autografting was performed.

Thirty additional patients were treated as in group 1, except that three minutes application of intraoperative sodium chloride 0.9% (normal saline solution) replaced

<table>
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<th>Group 2</th>
<th>Group 3</th>
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<td>Conjunctival autograft only</td>
<td>Normal saline solution</td>
<td>Combined MMC + conjunctival autograft</td>
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<td>Mean follow-up (mo)</td>
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MMC = mitomycin C.

*The number of patients, mean age during surgery, and the mean follow-up in the four study groups were identical.

FIGURE 1. Preoperative and postoperative appearance in a patient with pterygium after combined conjunctival autografting and intraoperative mitomycin C 0.02% (group 4). (Top left) Primary pterygium in the left eye of a 48-year-old patient. (Top right) One week after surgery, the conjunctival graft is still hyperemic and mildly edematous, but well apposed with sutures to the surrounding conjunctiva. (Bottom left) Magnification of the graft area, showing a beginning of anastomotic connections of the graft to the surrounding conjunctival vasculature. (Bottom right) Three months postoperatively the conjunctiva at the surgical site appears normal and quiet.
the MMC (group 3). Group 3 included 30 patients as follows: 19 patients who had refused the application of either MMC or the conjunctival autografting during the study period (July 1996 through June 1997) and an additional 11 consecutive patients who were treated in the same manner before the study began (July 1995 through June 1996). Group 4 included 30 consecutive patients who underwent pterygium excision and conjunctival autografting with intraoperative application of MMC 0.02% for one minute (before the transplantation procedure was performed). The procedures in group 4 were performed during the years 2001 and 2002.

Preoperatively, each patient underwent a complete eye examination. The inclusion criteria were age above 21 years and a primary fleshy or growing pterygium that invaded more than 2 mm into the cornea (Figure 1, Top left). We excluded patients with atrophic primary pterygia, dry eyes (determined by Schirmer I test), significant blepharitis, or any ocular, immune, or systemic diseases.

All the surgeries were performed on an outpatient basis at Hadassah University Hospital, Jerusalem, by two surgeons (J.F.-P. and M.I.), who equally performed the surgical procedures in each of the four groups. The procedure included topical anesthesia with benoxinate hydrochloride 0.4%. The pterygium was dissected from the cornea using a Beaver 64 surgical blade. The body of the pterygium, including the adjacent Tenon’s capsule, was dissected from the overlying conjunctiva, keeping the conjunctiva intact as much as possible (Figure 2, 1st and 2nd panels). Then the pterygium body was dissected from the underlying conjunctiva and thereafter excised. A 2 × 5-mm sponge was soaked in a solution of MMC 0.02% (in group 1) or in saline solution (in group 3) until its maximal absorbance capacity. The sponge was placed over the exposed sclera and the adjacent cornea. The conjunctiva was pulled over the sponge with 0.12-mm forceps, and the sponge was held in contact with the sclera and conjunctival tissue for three minutes (Figure 2, 4th panel). Thereafter the sponge was removed and the ocular tissue was washed with 15 ml of saline solution. Several 10–0 nylon sutures secured the conjunctiva to the sclera, leaving at least 1 mm of bare sclera (Figure 2, 3rd panel). Sutures were removed one week after the surgery.

Free conjunctival autografting after pterygium excision (group 2) was performed as follows: the desired size of the conjunctiva under the upper eyelid was marked (according to the size of the bare sclera defect), inflated with 0.5 ml of balanced salt solution, and excised. The excised tissue was placed on the bare sclera and tightly sutured to the sclera.

**FIGURE 2.** Surgical steps in pterygium surgery employed in the four study groups. (1st panel) Excision of pterygium is performed in all groups by dissection of the pterygium head from the cornea, followed by separation of the pterygium body from the overlying conjunctiva and from the sclera. (2nd panel) Following removal of the pterygium, the overlying conjunctiva remains intact. (3rd panel) A sponge on mitomycin C 0.2 mg/ml (group 1) or saline (group 3) is placed between the bare sclera and the conjunctiva for three minutes. (4th panel) After irrigation, the remaining conjunctiva is sutured to the sclera with interrupted 10–0 nylon sutures (groups 1 and 3). (5th panel) A free conjunctival autograft is taken from the upper bulbar conjunctiva and sutured to the bare sclera and surrounding conjunctiva (groups 2 and 4).
and the limbal area with 10–0 nylon stitches. Finally, the autograft edges were sutured to the conjunctiva all around (Figure 1, Top right and Bottom left, Figure 2, 5th panel) to speed the formation of anastomosis between blood vessels of the conjunctiva and the free graft. Topical antibiotics and corticosteroids were instilled and followed by eye pressure patching.

Combined MMC and free conjunctival autografting (group 4) was performed by removing the pterygium while keeping the overlying conjunctiva intact (as in group 1), followed by application of a sponge soaked in MMC 0.02% for 1 minute and irrigation. This was followed by suturing the remaining conjunctival edge at 4 to 5 mm from the limbus, excising a free conjunctival autograft from the upper bulbar conjunctiva, and suturing the free graft between the edge of the sutured conjunctiva and limbus, as in group 2 (Figure 2, 5th panel).

Following the surgery, each patient was treated with topical corticosteroids four times daily; corticosteroids were tapered and discontinued after three months. Topical antibiotics were used until epithelialization of the wound was complete. Patients were examined at days 1, 7, 15, 30, and 90, and then at three-month intervals during the first year and at six-month intervals after one year. Recurrence was diagnosed when vessels invaded through the limbal area into the clear cornea.

χ² test was used for statistical analysis.

### RESULTS

PATIENTS’ AGES WERE BETWEEN 21 AND 76 YEARS (MEAN age 42.3 ± 11.7); there were 51 women and 69 men. The demographic data and the follow-up periods in the studied groups are presented in Table 1. Follow-up for all patients was longer than 13 months.

Postoperatively, the conjunctival autograft had mild to moderate edema, which subsided within the first three to four weeks. In both the MMC-treated and the nontreated autografts, the formation of anastomatic connections in the autotransplant started between weeks one and two postoperatively (Figure 1, Bottom left). Sutures were removed after 3 to 4 weeks, when anastomotic vessels were found all around the graft.

The pterygium recurred in two patients (6.6%) in group 1, in four patients (13.3%) in group 2, and in 14 patients (46.6%) in group 3, but there were no cases of recurrence of pterygium in group 4 (Figure 1, Bottom right). χ² analysis revealed a significant difference in the recurrence rate in group 4 compared with group 2 (P = .038) and group 3 (P < .0001) (Table 2). No significant difference was demonstrated between the recurrence rates of groups 1 and 4 (P = .15).

No significant complications were encountered in any of the groups. In one case in group 4, a significant focal inflammatory response during the first 10 postoperative days was associated with melting of 10% of the conjunctival transplant area. This occurred as a result of conjunctival swelling over the flap with formation of a dellen-like dry area. The process was controlled by using a pressure patch and topical corticosteroids eight times per day. In six cases, two in group 2 and four in group 4, a subconjunctival hemorrhage manifested at the end of the surgery or appeared within the first postoperative week. The subconjunctival hemorrhage subsided within two to three weeks and did not affect the conjunctival autotransplantation outcome.

Two patients in groups 1 and 2 had moderate elevations of intraocular pressure, which were treated with timolol 0.5% twice daily and by replacing dexamethasone phosphate 0.1% with fluorometholone 0.1%.

### DISCUSSION

PTERYGIUM SURGERY HAS CHANGED OVER THE PAST DECADE, and several techniques are now available for the ophthalmic surgeon to choose from. Our study presents some of these techniques, which were employed at our institute, and reflects our efforts to improve the efficacy of the procedure by minimizing the recurrence rate and to address concerns regarding the safety of MMC. By com-
bining two of the most widely used techniques in pterygium surgery, namely, free conjunctival autografting and the intraoperative use of MMC, we have further reduced the recurrence rate and found a minimal number of postoperative complications.

MMC acts as an alkylating agent and causes irreversible damage to the DNA structures of the cell. In pterygium surgery, daily administration and single intraoperative use of a variety of MMC doses have been reported. However, the safest dosage of MMC that can prevent the recurrence of pterygium without causing complications is still unknown. Postoperative use of topical MMC is not recommended because of a possible drug misuse, which may cause severe ocular complications such as scleromalacia, corneal perforation, glaucoma, iritis, pain, and punctate keratopathy.

Single intraoperative use of MMC is safer than postoperative topical daily application. It has been reported since 1994. Our 10 years' experience with the use of MMC indicated its efficacy and safety. The recurrence rate of primary pterygia was approximately 6%, and only mild complications such as superficial punctate keratopathy and mild avascularity of the bare sclera area were observed. In addition, we have recently demonstrated a normal scleral thickness and a normal conjunctival epithelial phenotype at the surgical site more than six years after pterygium surgery with MMC. When bare sclera technique is performed in a patient with an otherwise normal ocular surface, the epithelialization of the wound area is usually completed within 7 to 14 days. Intact epithelium over the operated area is necessary to prevent scleral melting after pterygium surgery when MMC is used. To prevent scleral melting, we keep the conjunctiva overlying the body of the pterygium and suture it back to the sclera at the end of the procedure.

To avoid severe ocular complications, all patients with abnormal ocular surface who are at greater risk for a delay of epithelialization or excessive inflammation, such as patients with immune disorders, blepharitis, or dry eyes, were excluded from our studies. Furthermore, postoperatively, we are closely observing the patients until the epithelialization of the ocular surface is complete.

Many ophthalmologists prefer conjunctival autografting as an adjunct to pterygium excision. This procedure is time-consuming, requires a significant learning curve, and has equal or greater postoperative recurrence rates (as compared with MMC), but it is still the preferred approach because of the avoidance of MMC-related complications.

In the present study, we initially compared the recurrence rate of pterygium in patients with bare sclera and MMC (group 1) vs patients with free conjunctival autografting (group 2). We found that the conjunctival autograft group had more recurrences than the MMC group, but fewer recurrences compared with the patients treated with placebo (sodium chloride 0.9%; group 3). This observation suggested that the combination of contact inhibition by the autograft and the decrease of proliferation of fibroblasts by MMC may provide greater safety and efficacy. We have therefore added group 4 (free conjunctival autograft combined with one-minute application of MMC) to complete the original study. We found no recurrence of primary pterygium in 30 eyes of patients in group 4. To our best knowledge, this is the first report that compares the combined use of conjunctival autografting and intraoperative MMC with three other techniques for pterygium excision. In our report, conjunctival autografting combined with intraoperative one-minute application of MMC 0.02% (group 4) was not more effective than conjunctival autografting alone (group 2) (P = .038) but three minutes of intraoperative MMC 0.02% alone (group 1). The additive effect of one minute of MMC was sufficient to significantly improve the outcome of conjunctival autografting. Looking at the trend of the recurrence rates, larger groups might prove the greater efficacy of combined autografting and MMC application as compared with adjunctive MMC alone. One of the advantages of combined conjunctival autografting and MMC application is the reduced MMC exposure time of the sclera. Autografting with shorter drug application time or less concentrated doses of MMC should be studied and might increase the safety of the procedure.

We are aware of a possible bias in our study, which may have been caused by not randomizing all of the four treatment options at the same time, and by having the different procedures performed during different time periods. However, we do feel that our groups are comparable, because most of the surgical technique, including the method of tissue dissection, which is crucial for the success of the surgery, was consistently performed in all patients using the same principles. The great strength of our study is having the different procedures performed by the same surgeons on the same population, under the same setting for a period of a decade. This offers a unique opportunity to see how we have modified our surgical approach to pterygium excision over the span of time. In modern ophthalmology, bias may occur in many studies because of modifications of surgical approaches to various problems over a period of many years.

We have decided to include the bare sclera technique, although this technique is not acceptable today, because this forms the basis for our understanding of the recurrence rate in our population. Procedures with the bare sclera technique were performed at a time when MMC was still not widely accepted, and the procedure was one of the widely used techniques by many surgeons who were concerned about the use of MMC and were reluctant to use free conjunctival autografts in patients who may need the conjunctiva for future surgical procedures. The 50% rate of recurrence has been repeatedly shown in all of our previous studies.
Although the complications in group 4 were mild, there was a case of partial melting of the conjunctival transplant (1.0 × 1.5 mm), which might be MMC-related. The conjunctiva adjacent to the transplant was inflamed and swollen, causing a dellen-like formation with conjunctival flap dryness, epithelial defect, and melting of the corner of the transplant. Finally, the inflammation subsided with excessive use of topical corticosteroids and eye patching.

We feel that an appropriate surgical technique is essential for a successful outcome. Stretching and tightening of the autotransplant to the sclera and optimal apposition by sutures of the conjunctival autotransplant edges to the surrounding conjunctiva (Figure 1, Top right) are important for faster formation of anastomotic vessels, faster healing, avoidance of granuloma formation, and prevention of autograft shrinkage or failure. We believe that the most important surgical factor in reducing recurrence and preventing complications is covering the bare sclera with conjunctival tissue. Rubinfeld and Stein26 found that closing the conjunctiva with a sliding flap after intraoperative application of MMC reduced the recurrence rate from 44% (without MMC) to 2.7%. On the basis of our study and data from other reports, we can hypothesize that the combined effect of the antiproliferative property of MMC and the contact inhibition effect of the conjunctival transplantation may be beneficial in pterygium surgery. We believe that the severe complications of topical MMC use are greatly reduced by decreasing the exposure time of MMC to only one minute, by covering the sclera with normal conjunctival tissue, and by formation of a well-vascularized ocular surface.

Other studies support the low rates of pterygium recurrences and complications following conjunctival autografting with adjunctive MMC use. Wong and Law19 reported 76 patients with primary pterygium who were treated with conjunctival autografting and intraoperative MMC 0.025% for 1 minute and had recurrence rate of 9.2%, not different from patients treated with conjunctival autografting only (18.4%). However, when the patients with the most severe pterygia were compared, those who had combined conjunctival autografting and MMC did better (P = .03). The reported complications included pyogenic granulomas, conjunctival thickening, and conjunctival injection.19 Murlu and associates17 reported 40 eyes with recurrent pterygium treated by conjunctial autotransplantation and intraoperative MMC 0.02% for three minutes. The recurrence rate was 12.5%, not different from that with transplantation of conjunctival graft with limbal cells (14.6%). A short-term superficial keratopathy in 40% of the patients and contraction of one flap were the only complications reported. In another series of 46 patients undergoing pterygium excision with intraoperative MMC 0.02% for two minutes combined with free conjunctival autograft, only one recurrence (2%) was reported.20 In that series, hemorrhage under the graft appeared in five patients and resolved spontaneously, and one eye developed a mild symblepharon.

Our data show that conjunctival autografting combined with an intraoperative low dose of MMC is an efficient method to manage primary pterygium, with further reduction of the recurrence rate compared with our previous experience with MMC alone, and compared with other methods practiced in the same setting, and with minimal complications. Refinements of our previous methods, including shorter MMC application, and covering the bare sclera with a free graft may increase the safety profile of this surgical procedure. Further long-term controlled studies are needed to support our findings.

REFERENCES


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