Comparison of Mitomycin C and Limbal-Conjunctival Autograft in the Prevention of Pterygial Recurrence in Turkish Patients: A One-Year, Randomized, Assessor-Masked, Controlled Trial

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ABSTRACT

BACKGROUND: A pterygium is a fibrovascular overgrowth of degenerative bulbar conjunctival tissue that grows over the limbus onto the cornea. Although various approaches have been proposed for the treatment of pterygium, the common problem after these treatments is recurrence.

OBJECTIVES: The goals of this study were to compare the efficacy of mitomycin C (MMC) and limbal-conjunctival autograft (LCAD) in preventing recurrence of primary pterygia and to monitor long-term adverse effects (AEs).

METHODS: Patients undergoing pterygium surgery between February 2006 and May 2007 were assessed prospectively and randomly divided into 2 groups using a random number table. The MMC group underwent pterygium excision and received 0.02% MMC intraoperatively for 2 minutes. The LCAD group underwent pterygium excision and LCAD. Recurrence and AE rates of the 2 treatments were compared during the 1-year follow-up period. Assessors for pterygial recurrence were masked to treatment group.

RESULTS: One hundred thirteen eyes (57 patients in the MMC group and 56 patients in the LCAD group) were included in the study. Thirteen of the patients (7 in the MMC group and 6 in the LCAD group) were withdrawn due to irregular attendance at follow-up visits or lack of sufficient dose and duration for postoperative topical antibiotic and steroid administration; their data were excluded from analysis. Fifty patients (MMC group: 26 men, 24 women; mean [SD] age, 48.0 [12.3] years; age range, 30–73 years; LCAD group: 27 men, 23 women; mean age, 49.0 [12.6] years; age range, 28–71 years) in each group completed the study. The mean (SD) length of the pterygium across the limbus was similar in the MMC group and the LCAD group (4.18 [1.27] vs 4.07 [1.24] mm). The mean follow-up period was also similar in the 2 groups (16.0 [1.9] vs 15.0 [1.7] months). The rate of recurrence was significantly greater in the MMC group than in the LCAD group (10 [20.0%] vs 2 [4.0%] patients; \( P = 0.035 \)). Seven patients (14.0%) in the MMC group experienced AEs: conjunctival cyst (3 patients), symblepharon (2), conjunctival granuloma (1), and dellen (1).
the LCAU group, 1 patient (2.0%; \( P = 0.032 \) vs MMC group) experienced permanent graft edema. All patients in the LCAU group experienced transient graft edema, with recovery occurring in 3 to 4 weeks. There were no intraoperative complications and there was no graft rejection.

**Conclusions:** Recurrence and postoperative AEs were less frequently observed in primary excision with LCAU than with MMC in these Turkish patients who completed the study. This study found that pterygium excision with LCAU was well tolerated and effective in these patients. (Curr Ther Res Clin Exp. 2009;70:274–281) © 2009 Excerpta Medica Inc.

**Key words:** mitomycin C, limbal-conjunctival autograft, pterygium.

**Introduction**

A pterygium is a fibrovascular overgrowth of degenerative bulbar conjunctival tissue growing over the limbus onto the cornea. The disease occurs worldwide, although it is particularly common in tropical and subtropical countries.\(^1\) Pterygium causes chronic irritation, impaired cosmetic appearance, and decreased vision secondary to growth over the pupillary axis, induced astigmatism, or disruption of the precorneal tear film.\(^2\) Although various approaches (eg, surgical procedures, \( \beta \)-irradiation, laser treatments, and medications) have been proposed for the treatment of pterygium, a common problem after these treatments is recurrence.\(^3\) Recurrence rates of simple excision without adjuvant treatment in pterygium surgery have been reported to be 24% to 89%.\(^4\)

Mitomycin C (MMC) is an alkalizing agent that inhibits DNA synthesis, resulting in long-term inhibition of Tenon's fibroblast proliferation.\(^5\) MMC has been reported to be effective in preventing pterygial recurrence.\(^5\)–\(^7\) Its use in pterygium surgery was first reported in Japan in 1963\(^8\) and in the United States in 1988.\(^9\) Since then, it has been described in numerous studies as an effective adjunct in reducing the recurrence rate of pterygium after excision.\(^5\)–\(^7\),\(^9\) However, serious complications varying from scleral thinning to scleral necrosis have been observed after the use of MMC.\(^10\)

Limbal-conjunctival autograft (LCAU) is an alternative adjuvant treatment in pterygium surgery.\(^11\) Conjunctival autografting is time consuming and requires a significant learning curve,\(^12\) but it may be the preferred approach because it is not associated with MMC-related adverse effects (AEs).\(^13\) In 1985, Kenyon et al\(^14\) reported the first study using conjunctival autograft transplantation. The authors found a 7.3% secondary recurrence rate in patients with recurrent pterygium, whereas there was no recurrence with primary pterygium. Using the same technique, Lewallen\(^15\) reported a 21% recurrence rate for primary pterygium. In 1989, Tseng\(^16\) reported the limbus to be a distinct cellular structure, lying between the corneal and conjunctival epithelium, that contains stem cells that are vital for normal corneal epithelial regeneration and that prevent the growth of conjunctival epithelium onto the cornea through contact inhibition.

Although the pathogenesis of pterygium is still unclear, destruction of limbal stem cells by ultraviolet light exposure can result in pterygia.\(^17\) Because limbal stem-cell
injury is considered an etiologic factor of pterygium, stem cell transplantation by LCAU is recommended for both primary and recurrent pterygia.\textsuperscript{17} For this reason, LCAU has been recommended to prevent recurrences in primary and recurrent pterygium surgery.\textsuperscript{17} Recurrence rates after LCAU have been reported to be 2\% to 33\% in primary and recurrent pterygial surgery.\textsuperscript{18-20} Limbal stem cells prohibit excessive proliferation of conjunctival tissue and act like a barrier against the development of pterygia. The inclusion of limbal epithelium in a conjunctival graft restores the barrier function of the limbus. Studies have reported the effectiveness of LCAU in preventing pterygial recurrence.\textsuperscript{14-16} LCAU has been reported to be more effective than MMC in the prevention of recurrence in pterygium surgery, suggesting that LCAU might reduce rates of recurrence and complications.\textsuperscript{21}

The goals of this study were to compare the efficacy of MMC and LCAU in preventing recurrence of primary pterygia and to monitor long-term AEs.

**PATIENTS AND METHODS**

This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment. Institutional review board approval was obtained from Diyarbakir Training and Research Hospital (Diyarbakir, Turkey).

Patients were eligible for the study if they were aged >25 years and had a primary fleshy or growing pterygium that invaded >2 mm into the cornea. Patients were excluded from the study if they had a history of pterygium surgery, limbal stem-cell failure, ocular-surface disease, atrophic primary pterygium, previous limbal surgery, double-head pterygium, dry eyes, significant blepharitis, or any ocular, immune, or systemic disease.

Consecutive patients who met the inclusion criteria and who were undergoing excision of a primary pterygium between February 2006 and May 2007 were randomized into 2 treatment groups using a random number table.

Preoperatively, each patient underwent a detailed examination that included visual acuity, intraocular pressure, extraocular movements, biomicroscopy, documentation of pterygium size, and dilated funduscopy. On completion of pterygium excision, patients in 1 group received a single intraoperative dose of 0.02\% MMC (0.2 mg/mL) for 2 minutes; patients in the other group underwent an LCAU.

One surgeon (S.A.) performed the MMC procedures and another (Z.O.Y.) conducted the LCAU procedures, all of which were performed on an outpatient basis. The procedure included topical anesthesia with 0.4\% benoxinate hydrochloride. In the MMC group, the pterygium head was excised from the cornea with a disposable crescent knife. The conjunctival epithelium covering the body of the pterygium was separated from the pterygium body with spring-action scissors. The pterygium body was then separated from the episclera and the medial rectus fascia and excised, leaving the overlying conjunctiva intact. A sponge soaked in a solution of MMC 0.2 mg/mL was applied to the excisional area for 2 minutes. This was followed by copious irrigation of the space between the conjunctiva and the sclera with 20 to 30 mL of balanced saline solution. The conjunctiva was then sutured to the sclera with...
∼2 separated 10-0 polyglactin sutures, leaving an area of 2 mm of bare sclera between the conjunctival edge and the limbus.

In the LCAU group, the pterygium was separated from the cornea using a disposable knife. Conjunctival tissue was dissected. Pterygial tissue and subconjunctival Tenon's capsule was excised and the recipient bed was prepared for graft application. A free conjunctival graft prepared from superotemporal conjunctival tissue was dissected from the limbus at a thickness of 1 mm along the cornea. The LCAU was 1 mm wider than the recipient bed and the limbus was sutured using 10-0 nylon suture material.

After surgery, each patient was treated with a topical corticosteroid (prednisolone acetate 1%) 4 times daily; the corticosteroids were tapered and discontinued after 3 months. A topical antibiotic (ciprofloxacin) was used until epithelialization of the wound was complete. The topical corticosteroid and antibiotic therapies were the same for both groups, as was the follow-up. Patients were examined on days 1, 7, 15, 30, and 90 and then at 3-month intervals for ~1 year. Recurrence of the pterygium was assessed by another researcher (I.C.) who was masked to the treatment group.

Slit-lamp biomicroscopy was performed to evaluate the final clinical outcome after pterygium surgery. Pterygial recurrence was graded using a 4-point scale: 1 = normal appearance of the surgical site; 2 = the presence of fine episcleral vessels in the excised area extending to the limbus, but without any fibrous tissue; 3 = fibrovascular tissue in the excised area reaching to the limbus, but not invading the cornea; and 4 = a true corneal recurrence, with fibrovascular tissue invading the cornea.

**Statistical Analysis**

The t test was used to analyze recurrence rates. $P < 0.05$ was considered statistically significant. Only the patients who completed the study were included in the analysis.

**RESULTS**

One hundred thirteen eyes (57 patients in the MMC group, 56 patients in the LCAU group) were included in the study. Thirteen of the patients (7 in the MMC group, 6 in the LCAU group) were withdrawn due to irregular attendance at follow-up visits or lack of sufficient dose and duration for postoperative topical antibiotic and steroid administration. Fifty patients (MMC group: 26 men, 24 women; mean [SD] age, 48.0 [12.3] years; age range, 30–73 years; LCAU group: 27 men, 23 women; mean age, 49.0 [12.6] years; age range, 28–71 years) in each group completed the study. The 2 groups were similar in terms of demographic and clinical characteristics. The mean (SD) length of the pterygium across the limbus was similar in the MMC group and the LCAU group (4.18 [1.27] vs 4.07 [1.24] mm). The mean follow-up period was also similar in the 2 groups (16.0 [1.9] vs 15.0 [1.7] months) (Table I).

The rate of recurrence for pterygium was significantly higher in the MMC group than the LCAU group (10 [20%] vs 2 [4%] patients; $P = 0.035$). In the MMC group, pterygium recurrence was observed at month 3 in 1 patient, month 6 in 4 patients, month 8 in 3 patients, and month 12 in 2 patients. In the LCAU group, recurrence
Table I. Demographic and clinical characteristics of Turkish patients undergoing pterygial excision with intraoperative mitomycin C (MMC) or limbal-conjunctival autograft (LCAU) (N = 100).*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MMC Group (n = 50)</th>
<th>LCAU Group (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>48.0 (12.3)</td>
<td>49.0 (12.6)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>Range</td>
<td>30–73</td>
</tr>
<tr>
<td>Sex, no. (%)</td>
<td>Male</td>
<td>26 (52)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>24 (48)</td>
</tr>
<tr>
<td>Laterality, no. (%)</td>
<td>Right</td>
<td>28 (56)</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>22 (44)</td>
</tr>
<tr>
<td>Length of pterygium across limbus, mm</td>
<td>4.18 (1.27)</td>
<td>4.07 (1.24)</td>
</tr>
<tr>
<td>Follow-up, mean (SD), mo</td>
<td>16.0 (1.9)</td>
<td>15.0 (1.7)</td>
</tr>
</tbody>
</table>

*No significant between-group differences were observed.

was observed in 2 patients at month 3 (Table II). According to the 4-point recurrence scale, the 10 patients in the MMC group and 2 patients in the LCAU group who experienced recurrence were classified as follows: in the MMC group, 6 patients were grade 2, 3 patients were grade 3, and 1 patient was grade 4; in the LCAU group, 2 patients were grade 3.

In the MMC group, AEs were observed in 7 patients: conjunctival cyst (3 patients), symblepharon (2), conjunctival granuloma (1), and dellen (1). One patient in the LCAU group was found to have an AE (permanent graft edema) (Table III). None of the AEs were considered serious (eg, scleral thinning or scleral necrosis).

No intraoperative complications occurred in either group. All patients in both groups had mild symptoms of slight ocular pain, foreign body sensation, lacrimation, and photophobia during the first week after surgery. Postoperatively, patients in the LCAU group had mild to moderate edema that subsided within the first 3 to 4 weeks. Sutures were removed after 3 to 4 weeks when anastomotic vessels were found surrounding the graft. Subconjunctival hemorrhage subsided within 2 to 3 weeks in all patients and did not affect the conjunctival autograft outcome in any patient.

DISCUSSION

Pterygium surgery has changed over the past decade, and several techniques are now available. Our study presents some of these techniques, which were used at our institution, and reflects our efforts to improve the efficacy of the procedure by minimizing the recurrence rate and to address concerns regarding the tolerability of MMC.
Table II. Number of pterygial recurrences in Turkish patients who underwent pterygial excision with intraoperative mitomycin C (MMC) or limbal-conjunctival autograft (LCAU).

<table>
<thead>
<tr>
<th>Month of Follow-Up</th>
<th>MMC Group (n = 50)</th>
<th>LCAU Group (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>−</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>−</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>−</td>
</tr>
<tr>
<td>Total, no. (%)</td>
<td>10 (20)</td>
<td>2 (4)*</td>
</tr>
</tbody>
</table>

*P = 0.035 versus MMC.

MMC is one of the modalities used to reduce the recurrence rate in modern pterygium surgery. Intraoperative application of MMC is effective, and the drug is used regularly by ophthalmologists. MMC acts as an alkalizing agent that causes irreversible damage to the DNA structures of the cell. Administration of intraoperative MMC diminishes recurrence rates by avoiding fibrovascular proliferation. In pterygium surgery, daily administration and single intraoperative use of a variety of MMC doses have been reported. However, the dose of MMC that can prevent pterygial recurrence without causing complications is still unknown. Postoperative use of topical MMC is not recommended because of possible drug misuse, which may be associated with severe ocular complications (eg, scleromalacia, corneal perforation, glaucoma, iritis, pain, and punctate keratopathy). Single intraoperative use of MMC is better tolerated than postoperative topical daily application. All patients with an abnormal ocular surface placing them at increased risk for a delay of epithelialization or for

Table III. Postoperative adverse effects (AEs) in Turkish patients who underwent pterygial excision with intraoperative mitomycin C (MMC) or limbal-conjunctival autograft (LCAU).

<table>
<thead>
<tr>
<th>AE</th>
<th>MMC Group (n = 50)</th>
<th>LCAU Group (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctival cyst</td>
<td>3</td>
<td>−</td>
</tr>
<tr>
<td>Symblepharon</td>
<td>2</td>
<td>−</td>
</tr>
<tr>
<td>Conjunctival granuloma</td>
<td>1</td>
<td>−</td>
</tr>
<tr>
<td>Dellen</td>
<td>1</td>
<td>−</td>
</tr>
<tr>
<td>Permanent graft edema</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Ocular pain*</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Foreign body sensation*</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Photophobia*</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

*Ocular pain, foreign body sensation, and photophobia were transient AEs.
excessive inflammation (e.g., patients with immune disorders, blepharitis, or dry eyes) were excluded from our study in an attempt to avoid severe ocular complications. Furthermore, we observed the patients closely until epithelialization of the ocular surface was complete.25

The per-protocol design was a limitation of this study; 13 of the 113 patients who entered the study did not complete it. The small sample size was also a limitation. Further long-term, multicenter, randomized trials are needed to determine the best treatment method.

CONCLUSIONS
Recurrence and postoperative complications were less frequently observed in primary excision with LCAU than with MMC in these Turkish patients who completed the study. This study found that pterygium excision with LCAU was well tolerated and effective in these patients.

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