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Use of Adjunctive Mitomycin C in External Dacryocystorhinostomy Surgery Compared With Surgery Alone in Patients With Nasolacrimal Duct Obstruction: A Prospective, Double-Masked, Randomized, Controlled Trial

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ABSTRACT

BACKGROUND: The most common cause for the failure of external dacryocystorhinostomy (DCR) surgery is the formation of granulation tissue at the osteotomy site or common canaliculus.

OBJECTIVES: The aims of this study were to assess the efficacy of intraoperative adjunctive mitomycin C (MMC) treatment in external DCR surgery and to compare this procedure with the standard DCR procedure alone in the long term (1 year).

METHODS: In this prospective, double-masked, randomized, controlled trial, patients with primary acquired nasolacrimal duct obstruction were randomized (using a random number table) into 2 groups based on surgical procedure. In the MMC group, intraoperative adjunctive MMC 0.2 mg/mL was applied to the osteotomy site for 30 minutes. The control group underwent standard DCR procedure only. The results of the DCR surgeries were assessed using objective findings (eg, cessation of excessive tearing via nasolacrimal duct irrigation and the improvement in height of tear meniscus) and subjective symptoms (asking patients to describe the degree of tearing improvement). Both the patients and the researchers who were assessing the study outcomes were masked to treatment group.

RESULTS: One hundred eyes of 100 Turkish patients were assessed and equally randomized to the MMC (27 women, 23 men; mean [SD] age, 47.0 [7.6] years) and control (26 women, 24 men; mean age, 46.6 [8.8] years) groups. The follow-up period was not significantly different between the MMC and the control groups (13.1 [1.1] vs 13.2 [1.4] months). Significantly more eyes in the MMC group than the control group remained symptom-free throughout the 1-year follow-up period (45/50 [90%] vs 33/50 [66%]; $P = 0.005$). Significantly more patients in the control group than the MMC group had an improvement in symptoms at the 1-year follow-up

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(8/50 [16%] vs 2/50 [4%] eyes; $P = 0.005$). Based on the patency of the drainage system, the success rate was significantly greater in the MMC group than the control group (48/50 [96%] vs 42/50 [84%]; $P = 0.005$). Based on nasolacrimal duct irrigation, significantly fewer patients in the MMC group than the control group had an enclosed nasolacrimal duct (2/50 [4%] vs 8/50 [16%]). No adverse effects (eg, abnormal nasal bleeding, mucosal necrosis, infection) or any other surgical adverse events were observed.

CONCLUSIONS: In the management of these patients with primary acquired nasolacrimal duct obstruction, adjunctive intraoperative MMC application with standard DCR surgery had a significantly higher success rate than did standard DCR surgery alone. Further large, double-masked, randomized studies are needed to confirm these findings. (*Curr Ther Res Clin Exp.* 2009;70:267–273) © 2009 Excerpta Medica Inc.

KEY WORDS: dacryocystorhinostomy, nasolacrimal duct obstruction, mitomycin C.

INTRODUCTION

External dacryocystorhinostomy (DCR) has a success rate of ~90% in the management of nasolacrimal duct obstruction.[1,2] Other studies have reported success rates from 82% to 100% with this procedure.[3–5] Failure is frequently related to granulation formation at the osteotomy site or common canaliculus,[6,7] technical error,[8] or closure of the anastomosis site.[9] Fibrous tissue and granulation formation are associated with surgical failure because they diminish ostium size and lead to nonpatency.[6,10] Efforts should focus on inhibiting granulation tissue over the osteotomy site and anastomosed flaps to increase the surgical success rate.

Mitomycin C (MMC), an alkalizing antibiotic, acts by inhibiting DNA-dependent RNA synthesis and represents an alternative approach to prevent the development of fibrous tissue formation over the osteotomy site and the anastomosed flaps.[3] MMC has been reported to inhibit excessive fibrous tissue formation subsequent to trabeculectomy for glaucoma.[11] MMC may increase the surgical success rate of DCR by preventing both a decrease in ostium size and canalicular obstruction.[4,5,12]

Due to the potential for adverse effects (AEs), MMC is typically administered for brief durations (2–10 minutes) at doses of 0.2 to 0.4 mg/mL. It has been reported that 0.2 mg/mL MMC administered to an osteotomy site for 30 minutes might be favorable to increase success rates with no significant increase in AEs. The aims of this study were to assess the efficacy of intraoperative adjunctive MMC treatment in external DCR surgery and to compare this procedure with the standard DCR procedure alone in the long term (1 year).

PATIENTS AND METHODS

In this prospective, double-masked, randomized, controlled trial, patients with primary acquired nasolacrimal duct obstruction who were to undergo DCR surgery from 2005 to 2007 were divided into 2 groups based on the surgical procedure. The patients were randomized to treatment using a random number table. In the MMC

group, intraoperative adjunctive MMC 0.2 mg/mL was applied to the osteotomy site for 30 minutes. The control group underwent the standard DCR surgery only.

The exclusion criteria were as follows: aged <18 or >70 years, previous nasolacrimal duct surgery, morphologic or functional palpebral disorders, and secondary causes of nasolacrimal duct obstruction.

Written informed consent was obtained from all participants prior to surgery. Institutional review board approval was obtained from Diyarbakir Training and Research Hospital (Diyarbakir, Turkey).

Both objective findings and subjective reports were followed up for ~1 year after the surgery. Clinical assessments, including dacryocystography and endoscopic nasal examinations, were performed throughout the follow-up period.

In both groups, the standard DCR procedure[1,2] was carried out under local anesthesia consisting of lidocaine hydrochloride 20 mg and epinephrine 0.0125 mg/mL (Jetocain simplex®, Adeka, Izmir, Turkey) administered to the medial and lower canthus. Anesthesia of the nasal mucosa consisted of 2 mL cocaine 5% and adrenaline 1:100,000. An incision site of ~2 cm was marked over the anterior lacrimal crest starting just below the medial canthal tendon. The skin was incised and blunt dissection was performed until the periosteum overlying the anterior lacrimal crest was exposed. The periosteum was incised and elevated off the lacrimal sac fossa. The osteotomy was created over the lacrimal sac fossa using a Kerrison punch. In every case, the ostium was maintained at 15 × 15 mm along the superoinferior and anteroposterior axes. The nasal mucosa was cut with sharp-tipped scissors to form anterior and posterior mucosal flaps, then the posterior nasal and lacrimal sac flaps were joined with 6-0 Vicryl sutures (Ethicon Inc., Somerville, New Jersey). In the MMC group, a piece of 0.5 × 0.5-cm neurosurgical cottonoid with long silk strings saturated with 1 mL of MMC 0.2 mg/mL was placed over the anastomosed posterior flaps and osteotomy site. The silk strings were left protruding from the nasal cavity. The anterior nasal and lacrimal sac flaps were closed with 6-0 Vicryl sutures, in addition to closing the periosteum and the orbicularis muscle in separate layers. The skin incision was closed with a running 6-0 Prolene suture (Ethicon Inc.). The MMC-soaked cottonoid was removed transnasally by pulling out the silk string in the recovery room after an application time of 30 minutes.

In the control group, the same surgical procedures were performed, except that MMC and the silk cottonoid were not applied. The surgeries were performed by a single surgeon (Ş.A.). There was no contact between the surgeon and the researchers evaluating the study outcomes. The patients and the researchers were masked to the treatment.

Gentamicin 3% and dexamethasone eyedrops were administered postoperatively 4 times daily for 1 month and oral antibiotic treatment was administered for 7 days. Regular clinical examinations were carried out at 1 and 14 days and 1, 2, 3, 6, and 12 months postoperatively. At each visit, sterile saline was used for irrigation and the stitches were removed 14 days postsurgery.

Recording and follow-up of AEs were performed by another surgeon (S.S.) who was masked to treatment. AEs were evaluated by transcanalicular nasolacrimal irrigation

and transnasal endoscopic examination. *Success* was defined as being asymptomatic or having improvement in tearing and patency of drainage. At each visit, the success rate was evaluated objectively based on the patency of irrigation and subjectively by asking the patient about tearing.

Failure was defined as no improvement in tearing, consistency in the severity of symptoms, or nonpatency of the nasolacrimal duct.

The *t* and χ^2 tests were used for statistical analysis. $P < 0.05$ was considered statistically significant.

RESULTS

One hundred eyes of 100 Turkish patients were enrolled and equally randomized to the MMC (27 women, 23 men; mean [SD] age, 47.0 [7.6] years) or control (26 women, 24 men; mean age, 46.6 [8.8] years) groups. The follow-up period was not significantly different between the MMC and the control group (13.1 [1.1] months vs 13.2 [1.4] months) (Table).

Significantly more eyes in the MMC group than the control group remained symptom-free throughout the 1-year follow-up period (45/50 [90%] vs 33/50 [66%] of eyes; $P = 0.005$). Improvement in symptoms was achieved in significantly fewer patients in the MMC group than the control group (3 [6%] vs 9 [18%]; $P < 0.005$) at the 1-year follow-up visit. Significantly fewer eyes in the MMC group than the control group remained symptomatic (excess tearing) (2/50 [4%] vs 8/50 [16%]; $P = 0.005$). The success rate was significantly greater in the MMC group than the control group ($P < 0.005$). Based on the patency of the drainage system, the success rate was significantly greater in the MMC group than the control group (48/50 [96%] vs 42/50 [84%]; $P = 0.005$). The remaining 2 patients in the MMC group and 8 patients in the control group had nonpatency due to obstruction by granulation tissue at the osteotomy site and underwent revision endoscopic lacrimal surgery.

Table. Demographic and clinical characteristics of the study patients (N = 100).*

Characteristic	MMC Group (n = 50)	Control Group (n = 50)
Age, y		
Mean (SD)	47.0 (7.6)	46.6 (8.8)
Range	34–64	32–62
Sex, no. (%)		
Female	27 (54)	26 (52)
Male	23 (46)	24 (48)
Duration of symptoms, mean (SD), mo	9.2 (1.9)	8.5 (1.7)
Duration of follow-up, mean (SD), mo	13.1 (1.1)	13.2 (1.4)

MMC = mitomycin C.

*There were no statistically significant between-group differences.

Neither local nor systemic AEs (eg, nasal or gastrointestinal irritation) associated with MMC were reported. No patient experienced nasal bleeding, mucosal necrosis, or infection during the follow-up period. No AEs were observed.

DISCUSSION

Studies evaluating success and complication rates of MMC treatment for chronic nasolacrimal duct obstruction were found in the literature.[4] In a prospective, randomized, controlled study in 88 eyes with primary acquired nasolacrimal duct obstructions, Liao et al[4] assessed the efficacy of 0.2 mg/mL MMC applied to the osteotomy site for 30 minutes in DCR surgery. During the 10-month follow-up period, 95.5% (42/44) of patients in the MMC group were symptom-free, while 70.5% (31/44) of control group patients were symptom-free ($P < 0.05$). Improvement in symptoms was observed in 18% of patients during the follow-up period. The nonpatency rate in the MMC group and the control group was 4.5% and 11.4%, respectively ($P < 0.05$). Yeatts and Neves[13] reported patency of the nasolacrimal duct with external DCR and MMC 0.3 mg/mL for 3 minutes during the 14.6-month follow-up period. They evaluated the usefulness of a single intraoperative application of MMC in repeat DCR for membranous failure and stated that adjunctive use of MMC might increase the success rate of repeat DCR. In a study of intraoperative MMC with DCR, Kao et al[10] found that the osteotomy site was significantly larger in the MMC group than the control group (mean [SD], 27.10 [5.78] vs 10.63 [3.37] mm^2). Kao et al carried out their study in 15 eyes of 14 patients diagnosed with primary acquired nasolacrimal duct obstruction. Patients were assigned randomly to either the MMC or the control group. Surgical procedures in both groups were exactly the same, except that in the patients in the MMC group, a piece of neurosurgical cottonoid soaked with 0.2 mg/mL MMC was applied to the osteotomy site and then removed transnasally after 30 minutes. Endonasal findings were recorded at the completion of the surgery and at 1, 3, and 6 months after surgery for the 2 groups. Intraoperative MMC was effective in maintaining a larger osteotomy size. A statistically significant difference was noted at 6 months ($P < 0.05$). Ugurbas et al[14] studied the histopathologic effects of MMC on transnasal DCR by soaking the osteotomy site in MMC 0.5 mg/mL for 2.5 minutes. A 0.5-mg/mL solution of MMC was applied to the osteotomy site for 2.5 minutes intraoperatively. Specimens from 4 patients were collected during surgery and at 15 days, 1 month, 3 months, and 6 months after surgery. The specimens were examined under light and electron transmission microscopy and were compared with control specimens. Light and electron microscopy found attenuated epithelium and looser, hypocellular subepithelial connective tissue in the MMC specimens. This finding suggests the efficacy of MMC application and indicates histopathologic evidence of the procedure. MMC is considered to be effective in decreasing the density and cellularity of mucosa and achieving higher success rates (improvement in tearing condition and lesser fibrous tissue formation) in DCR surgery. This result corresponds with the results of the study carried out by Yildirim et al.[6]

In our study, the 2 groups included the same number of eyes. There was no significant difference in the mean ages of the patients in the 2 groups. Forty-five eyes in the

MMC group and 33 eyes in the control group remained symptom-free throughout the 1-year follow-up period. Improvement in symptoms was achieved in 3 eyes in the MMC group and 9 eyes in the control group. Based on the patency of the drainage system, the success rate was significantly greater in the MMC group than the control group. The remaining 2 patients in the MMC group and 8 patients in the control group had nonpatency due to obstruction at the osteotomy site.

The effectiveness of intraoperative MMC treatment in DCR surgery was reported by You and Fang.[15] Fifty eyes were included in the study and were divided into 3 groups. MMC 0.2 and 0.5 mg/mL were administered for 5 minutes and the results were compared with those of a conventional DCR surgery group. A significant difference was found between the MMC-treated patients and the control group in patency rate and osteotomy size; however, no significant difference was found between the 2 MMC groups. Ugurbas et al[14] found that MMC 0.5 mg/mL for 5 and 2.5 minutes favorably affected healing at the osteotomy site. In our study, we administered MMC 0.2 mg/mL for 30 minutes to maximize the inhibition of fibrosis. No significant increase in the duration of surgery was noted due to MMC application.

Pterygium and glaucoma filtration surgeries are associated with some AEs (eg, corneal ulcus or perforation, scleral calcification, secondary cataract, endophthalmitis, hypotony, and maculopathy).[16,17] We observed no serious AEs associated with MMC administration, such as mucosal necrosis, abnormal nasal bleeding, severe infections, or gastrointestinal bleeding.[3,10]

Limitations of this study were its small sample size and the lack of elderly patients in the study population. Further large, double-masked, randomized studies are needed to confirm these findings.

CONCLUSION

In the management of these patients with primary acquired nasolacrimal duct obstruction, adjunctive intraoperative MMC application with standard DCR surgery had a significantly higher success rate than did standard DCR surgery alone.

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