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RHINOLOGY

Efficacy of adjunctive mitomycin C in transcanalicular diode laser dacryocystorhinostomy

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Abstract The objective of the study was to compare the success rate of transcanalicular laser dacryocystorhinostomy (TCL-DCR) with or without the use of adjunctive mitomycin C (MMC) in cases with primary nasolacrimal duct obstruction (NLDO). This retrospective study was comprised of 68 patients with uncomplicated primary NLDO. There were two groups in the study: the Group 1 ($n = 35$) patients underwent TCL-DCR surgery with MMC and the Group 2 ($n = 33$) patients underwent TCL-DCR surgery without MMC. All patients had bicanalicular silicone tube intubation. The main outcome measures were patent osteotomy as visualized endoscopically and patent nasolacrimal irrigation. The follow-up period was 12 months. All patients had unilateral TCL-DCR with silicone tube intubation. Six months following surgery, the silicone tubes were removed. At the final evaluation, success rates were 80 % in Group 1 and 78.8 % in Group 2. There was no statistically significant difference between the two groups ($p = 0.52$). No complications related to MMC usage were recorded during the study period. Intraoperative use of MMC has no beneficial effect on the success rate in TCL-DCR.

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Introduction

The gold standard in the treatment for nasolacrimal duct obstruction (NLDO) is external dacryocystorhinostomy (DCR) to restore patency of the lacrimal outflow system [1]. Although the classical external approach has the highest success rate and is widely accepted, the search continues for new techniques to reduce surgical trauma, operative time, and recovery time. The latest development in DCR surgery is transcanalicular diode laser DCR (TCL-DCR) [2]. However, the success rate of TCL-DCR is lower when compared to classical external DCR [1]. Because the most frequent causes of DCR failure are obstruction of the common canaliculus and osteotomy site, approaches that decrease fibrosis formation may increase the surgical success rate.

Mitomycin C (MMC) is an antineoplastic agent isolated from *Streptomyces caespitosus*. MMC inhibits DNA synthesis and cell proliferation, thereby decreasing collagen synthesis by fibroblasts and suppressing resultant fibrosis and scarring. To prevent excessive scar formation, MMC has been used as a surgical adjuvant in glaucoma and pterygium surgery [3–5]. Then, its use has been described in lacrimal drainage surgery [6–8]. The probable benefit of MMC as a surgical adjuvant is thought to be related to its potent inhibition of fibroblast proliferation. Intraoperative use of MMC in lacrimal drainage surgery can minimize postoperative fibrosis and granulations, thereby achieving a bigger postoperative ostium.

The purpose of this retrospective study was to compare the surgical outcomes of TCL-DCR surgery with and

without MMC in the treatment of a series of 68 patients with primary uncomplicated nasolacrimal duct obstruction.

Materials and methods

Subjects and design

This retrospective and comparative study included a series of 68 patients with acquired NLDO who underwent TCL-DCR surgery with bicanalicular silicone tube intubation at Istanbul Medipol University, Department of Ophthalmology, between March 2012 and September 2013. The study was carried out in agreement with the Declaration of Helsinki, and the ethics committee approved the study. All of the patients provided written informed consent and were thoroughly informed about the advantages and disadvantages of all available surgical interventions for NLDO. A retrospective review was made according to the intraoperative use of MMC. Group 1 comprised 35 patients who underwent TCL-DCR surgery with MMC, and Group 2 comprised 33 patients who underwent TCL-DCR surgery without MMC. In each case, a complete ophthalmic examination was performed to rule out other causes of epiphora. Lacrimal irrigation was performed to confirm the nasolacrimal duct obstruction, and patients underwent both contrast dacryocystorhinography and nasolacrimal system scintigraphy or nasolacrimal system scintigraphy alone to determine the exact level of obstruction. All patients had also undergone a rhinologic examination to rule out concomitant nasal pathology. The inclusion criteria for the study were: (1) symptomatic epiphora due to primary nasolacrimal duct obstruction proven by nasolacrimal duct irrigation; (2) aged over 18 years; (3) no history of naso-orbital trauma; (4) no history of previous nasolacrimal duct surgery; (5) no canalicular obstruction; (6) no concomitant nasal and septal pathology; (7) a follow-up at least 12 months. Patients with diabetes mellitus, eyelid, and eyelash abnormalities were excluded. Preoperative systemic screening was conducted for each patient.

Surgical procedure

All surgeries were performed by the same surgeon (MO) under general anesthesia. Topical nasal decongestant (xylometazoline nasal drops) was instilled four times at 15-min intervals 1 h before the operation. Vasoconstriction of nasal mucosa was achieved by applying gauze soaked in a 1:1 mixture of epinephrine 1:100,000. After dilatation of the superior and inferior lacrimal canaliculi with punctum dilators, 600-μm quartz Teflon fiber was inserted through the inferior lacrimal canaliculus with a red pilot beam light activated. Through a nasal endoscope, the pilot beam transillumination from the lacrimal sac was recognized and adjusted anteroinferiorly at the insertion point of the middle concha while visualizing the middle nasal meatus. Then, the laser beam was activated to create a fistula between the lacrimal sac and the nasal cavity. The laser used was a Multidiode SLPTM S30 Gallium Arsenide P diode laser (Intermedic, Lower Saxony, Germany) with a repetitive pulse mode of 980 nm. The laser settings were as follows: power 10 W, pulse length 90 ms, and pause between pulses 50 ms. Once the fistula was created, its orifice was enlarged at the endonasal side with additional laser pulses to reach a width of 10–10 mm. Following laser probe removal, diluted betadine irrigation was performed to ensure patency of the drainage system. A cottonoid soaked with MMC (Mitomycin-C Kyowa, 2 mg) at a concentration of 0.2 mg/ml was placed over the osteotomy site transnasally for 3 min in the Group 1. Mitomycin C was irrigated with 60 ml of saline solution. Finally, bicanalicular silicone intubation was performed in all patients: silicone extensions of the tube were tied to each other and then were left free in the nasal cavity. Tamponade was applied to the nasal cavity to ensure control of bleeding.

Postoperatively, all patients were prescribed a steroid nasal spray four times a day, as well as tobramycin/dexamethasone eye drops four times daily for 2 weeks following surgery. Additionally, oral antibiotic was prescribed for 7 days. Follow-up postoperative examinations were carried out on the first day, in the first week, in the first month, in the 3rd, 6th, and 12th months. Lacrimal irrigation and endoscopic evaluation were performed at each visit (with one exception: endoscopic evaluation was not performed on the first day). The silicone tube was removed 6 months after intubation. In follow-up visits, the patency of the lacrimal drainage system was checked. Surgical success was defined as patent osteotomy as visualized endoscopically and patent nasolacrimal irrigation.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences for Windows 16.0 program (SPSS, Chicago, IL). The normal distribution of the considered variables was first evaluated using the Shapiro–Wilk test. Descriptive statistics were represented as mean values and standard errors of the mean. Independent sample t test was used to compare the means between Group 1 and Group 2. The differences between the groups were analyzed by Chi-square tests. A p value of less than 0.05 was considered significant.

Results

A total of 68 patients were enrolled in the study. Group 1 and Group 2 consisted of 35 and 33 patients, respectively. The patients' demographics are presented in Table 1. The mean age of Group 1 was 49.4 ± 2.3, while the mean age of Group 2 was 52.2 ± 3.0. There were no statistically significant differences between the groups in terms of age, gender, and eye involvement ($p = 0.62$, $p = 0.73$, $p = 0.78$, respectively). NLDO was equal in both sides. All patients had unilateral TCL-DCR with bicanalicular silicone tube intubations. There were no complications during the operations. The mean surgical time for Groups 1 and 2 was 22.96 ± 2.15 and 16.54 ± 3.76 min (range 10–25 min in both groups), respectively. The mean surgical time was longer due to MMC application in Group 1, and there was a statistically significant difference among the groups ($p = 0.014$). The mean total laser energy of Groups 1 and 2 was 675.42 ± 59.18 and 674.09 ± 59.47 Joules, respectively (range 420–760 J in both groups). There was no statistically significant difference among the groups in terms of total laser energy ($p = 0.94$). After 1 week of surgery, 34 (97.1 %) eyes in the Group 1 and 31 (93.9 %) eyes in Group 2 had patent osteotomy and irrigation. This difference was statistically significant ($p = 0.031$). Success rate in groups (with or without MMC) during the follow-up are shown in Fig. 1. One month after the surgery, 32 (91.4 %) eyes in Group 1 and 28 (84.8 %) eyes in Group 2 had patent osteotomy and irrigation ($p = 0.028$). Three months after the surgery, 30 (85.7 %) eyes in Group 1 and 28 (84.8 %) eyes in Group 2 had patent osteotomy and irrigation ($p = 0.58$). Six months after surgery, the silicone tubes were removed. At that time, 29 (82.8 %) eyes in Group 1 and 27 (81.8 %) eyes in Group 2 had patent osteotomy and irrigation ($p = 0.52$). At month 12, 28 (80 %) eyes in Group 1 and 26 (78.8 %) eyes in Group 2 had patent osteotomy as seen endoscopically and patent nasolacrimal irrigation ($p = 0.52$). In Group 1, endoscopic examinations showed mucosal scarring around the osteotomized area, and reobstruction occurred in seven of the patients. In these cases, the result was evaluated as a failure, and reobstruction occurred between 1 and 3 months, postoperatively, in five patients and between 6 and 12 months in two patients. In Group 2, endoscopic examinations showed scarring of the internal ostium in seven of the patients. Reobstruction occurred at the 1st month in five patients, and between 3 and 6 months in two patients. We did not record any complication related to the use of mitomycin C such as bleeding, poor epithelization, mucosal or bone necrosis or infection. Additionally, there were no other complications such as erosion of the punctum, fistulation to skin, and removal of the tubes. The follow-up period was 12 months.

Table 1 Demographics of patients

	Group 1	Group 2
Number of patients	35	33
Mean age (years ± SD)	49.4 ± 2.3	52.2 ± 3.0
Male	17	16
Female	18	17
Laterality		
Right side	14	15
Left side	16	15

SD standard deviation

Discussion

In the present study, we evaluated the efficacy and safety of MMC in TCL-DCR. In both groups, we used silicone tube intubation, which was removed at 6 months. The final success rate in Group 1 was 80 %, compared to 78.8 % in Group 2. Although we achieved a higher success rate with MMC application, the difference was not statistically significant. There were a total of 14 failures in this study: 7 in Group 1 and 7 in Group 2. All failures were related to the mucosal scarring around the osteotomy site. The dosage of intraoperative MMC used in this study was 0.2 mg/ml for 3 min. We did not observe any complications related to MMC such as bleeding, poor epithelization, mucosal or bone necrosis or infection.

TCL-DCR is a minimally invasive surgical procedure, which has the great advantage of accessing the operating field through anatomic pathways. It minimizes trauma to surrounding tissue, avoids injury to medial cantus, provides no external surgical skin scars, and preserves the pumping mechanism of the orbicularis muscle. In addition, TCL-DCR causes minimum pain and minimum nasal bleeding. It is also easier and faster to perform compared to the classical dacryocystorhinostomy. Silicon tube intubation with DCR surgery is used to prevent the blocking of the lacrimal passage and to provide epithelization. But conventional dacryocystorhinostomy still has the highest success rate over TCL-DCR. Several factors may explain the difference: sump phenomenon, adhesion formation, osteotomy size, and phimosis of the ostium have all been implicated in TCL-DCR's lower success rate [1, 2, 6–9].

MMC inhibits DNA synthesis and cell proliferation, thereby decreasing collagen synthesis by fibroblasts and suppressing resultant fibrosis and scarring. It has been successfully used in many ophthalmic procedures such as trabeculectomy and pterygium surgery to enhance the surgical rate [3–5]. Many studies have investigated adjunctive MMC for external or endoscopic DCR to augment the surgical success rate [6–17]. Some of these

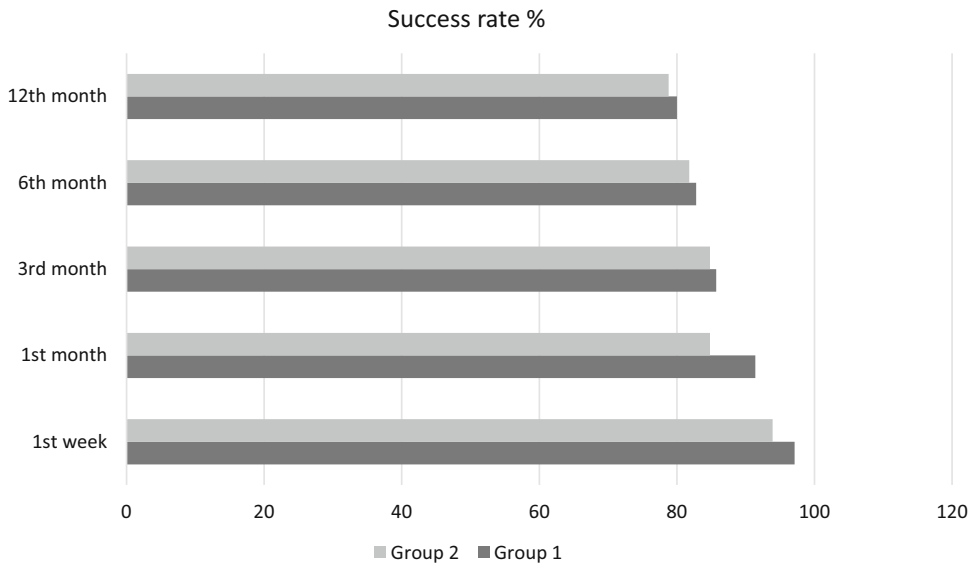

Fig. 1 Success rate in groups (with or without MMC) during the follow-up

reports stated the efficacy of MMC, others stated the same equivalence. Kao et al. used MMC in external DCR and reported a 100 % success rate in the MMC group versus 88 % in the control group [6]. Similarly, Liao et al. used MMC in conventional DCR and found that MMC was safe and increased the patency success rate by maintaining a larger osteotomy size at 6 months [7]. After these published reports, the use of MMC was extended to endoscopic DCR. Ugurbas et al. were one of the first to study the histopathology following the use of MMC intraoperatively in endoscopic endonasal DCR [8]. The authors demonstrated that topical use of mitomycin C may enhance the success of surgery by decreasing in density and cellularity of mucosa. Dolmetsch et al. used MMC in non-laser endoscopic DCR and reported a success rate of 95 % with no complications related to MMC usage [10]. Similarly, Camara et al. evaluated the effect of MMC in laser endoscopic DCR and achieved a success rate of 99.2 % in the MMC group versus 89.6 % in the control group [11]. Following these reports, Henson et al. reported an 87.5 % success rate of MMC in TCL-DCR at 18 months, but they used no control group; they stated that all failures were due to nasal osteotomy constriction [12]. The later studies by Qin and Ozkiris also found that adjunctive use of intraoperative MMC could increase the success rates [13, 14]. On the other hand, Tirakunwichcha et al. reported that there was no statistically significant difference in the success rates between the MMC group and controls [15]. Similarly, Prasannaraj et al. reported a success rate of 82.3 % when MMC was used and 85.7 % in the controls; there was no statistically significant difference in groups ($p > 0.05$) [16]. Then Gosh et al. reported a success rate of 80 % in patients with adjunctive MMC versus 86.67 % in the control group [17]. In the present study, we also found no statistically significant difference in the success rate between the two groups (with or without MMC). Varying concentrations, different routes of applications, and duration of MMC have been investigated in different studies, but there is still no agreement on this issue [18]. Ali et al. demonstrated that both topical and circumostial injection of MMC induced ultrastructural changes within fibroblasts. These changes included intracellular edema, pleomorphic and vesicular mitochondria, dilated smooth and rough endoplasmic reticulum, and chromatin condensation [19]. Laboratory tests on primary cultures of human nasal mucosal fibroblasts showed that application of MMC at 0.4 mg/ml over 5 min and 0.5 mg/ml over 3 min caused extensive death when compared with the controls. On the other hand, exposure to MMC at 0.2 mg/ml for 3 min prevented cell proliferation of fibroblast by inducing cell cycle arrest, without causing extensive apoptosis [20]. In the present study, we used a concentration of 0.2 mg/ml MMC for a duration of 3 min and did not observe any complications related to MMC such as bleeding, poor epithelization, mucosal or bone necrosis or infection.

As with all studies, our findings must be considered along with the limitations of the study. One possible weakness of the study is the small number in each group. Despite these limitations, there was no statistically significant difference at baseline with respect to age that can affect the surgical outcome. Further, all operations were performed by the same surgeon and the follow-up was enough to evaluate the surgical outcomes.

In conclusion, the data obtained from the present study suggest that MMC is safe but has no beneficial effect on the success rate in TCL-DCR. However, further prospective studies with larger sample sizes are necessary to determine the ultimate potential of MMC in TCL-DCR.

Compliance with ethical standards

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Conflict of interest Mustafa Ozsutcu, Özlem Balci, Cafer Tanrıverdi, and Goktug Demirci have nothing to declare.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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