Silicone Tube Intubation with Intraoperative Mitomycin C for Nasolacrimal Duct Obstruction in Adults: A Prospective Randomized Double-Masked Study

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Abstract

**Purpose:** To assess the efficacy of intraoperative mitomycin C (MMC) during silicone intubation (SI) as a substitute for dacryocystorhinostomy (DCR) in nasolacrimal duct (NLD) obstruction.

**Methods:** In a prospective, randomized, double-blind study, 88 candidates of DCR for NLD obstruction were randomly assigned into two groups of SI with application of either MMC (0.2 mg/ml for 2 minutes) or placebo.

**Results:** After a mean follow-up interval of 8 months, 25 of the 43 eyes in the MMC group and 21 of the 44 eyes in the placebo group had a successful outcome and were free of tearing and discharge (P=0.331). In patients with simple epiphora and less than 6 months of duration of symptoms, SI alone was effective in 83% of patients; MMC application during SI did not show additional benefit over SI alone in this group of patients. But in patients with simple epiphora and more than 6 months duration, the application of MMC during SI resulted in better efficacy compared to SI alone. The overall success rates in the patients with chronic dacryocystitis was lower (23%) compared to patients with epiphora only (63.7%).

**Conclusion:** SI alone could effectively substitute for a more extensive procedure such as DCR in patients with simple epiphora particularly in whom their symptoms has been newly developed. In cases with longer duration of symptoms of epiphora, application of MMC would increase the success rate significantly.

**Keywords:** silicone intubation, mitomycin C, dacryocystorhinostomy


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**Introduction**

Dacryocystorhinostomy (DCR) is the mainstay treatment for nasolacrimal duct (NLD) obstruction. The procedure yields success rates exceeding 90%, but long-term patency may be compromised by obstruction of the common canaliculus or closure of the osteotomy site by granulation tissue and scarring. On the other hand this procedure is relatively extensive and invasive. It is logical, cost effective, and beneficial to patients to have a simpler procedure performed whenever possible.

Silicone intubation (SI) is indicated in the treatment of congenital and acquired NLD obstructions, with a success rate ranging from 63% to 100%. This procedure is particularly successful in mild to moderate obstruction, and uncomplicated cases.

Since introduction by Chen, MMC has been used in many ocular procedures to reduce scarring and to enhance the success rate. Its application in lacrimal surgery has been studied by some authors. Liu and Bosley studied SI of the NLD with MMC but did not have beneficial results.

We carried out a randomized, double-masked, prospective study to evaluate the efficacy of MMC-treated SI technique in patients who may have undergone a DCR as an alternative procedure considering protocols of the Liu and Bosley study.

**Methods**

Ninety-three eyes from 87 consecutive patients with a chief symptom of tearing and discharge due to primary acquired and complete NLD obstruction who were potential candidate of DCR were included in our study between July 2003 and October 2005. Only patients with primary acquired NLD obstruction were included in the study. Patients with symptoms secondary to identifiable or treatable causes such as dry eyes, lid abnormalities (trichiasis, distichiasis, entropion, ectropion, lid laxity), glaucoma, refractive error, tumor of the eyelid, and secondary causes of NLD obstruction such as fractures of the facial bones, nose structural abnormalities, severe atrophic rhinitis, tumors of the lacrimal system, canalicular and common canalicular obstruction, and previously failed DCR were excluded.

Informed consent was obtained from all patients. Preoperative work-up including obtaining patient medical and ocular history, visual acuity, thorough slit-lamp examination of the conjunctiva and cornea to rule out possible ocular surface disorders, was performed. The eyelids were examined for proper closure and possible laxity or misdirected lashes. Whenever needed, Schirmer I and II tests, tear break-up time, Jones test I, or a dye disappearance test, and fluorescein staining were performed. Irrigation with saline solution revealed the nature and location of the obstruction.

Patients who were candidate for DCR were divided into two groups for alternate surgical plan including SI with application in a randomized, double-masked fashion of MMC or placebo, with the former receiving 0.2 mg/ml MMC for 2 minutes before SI. Each group was divided into 2 groups based on presence or absence of pus reflux.

**Surgical technique**

The procedure was performed under local anesthesia in all patients. Blunt-tipped probe was used to dilate and for probing of both the upper and lower puncta. A Crawford SI set (BD Visitec, 27 gauge) was used in all patients. If resistance was felt, its location was recorded. Probing of NLD with SI was abandoned if the resistance or obstruction was too difficult to overcome or if excessive bleeding or a hard blind bony pouch at the end of the nasal lacrimal duct was found (5 patients). In these patients, DCR was performed.

After overcoming the obstruction, the Crawford silicone was slightly withdrawn and while suctioning the nasal cavity, the masked medication was injected through other canalicule to the lacrimal system via the cannula attached to a 1-ml syringe. Care was taken so that there was no spill over the cornea, and constant corneal irrigation with saline solution was given during this period. The masked medication was left in the lacrimal system for 2 minutes, with occasional gentle massage of the lacrimal system over the sac area with a cotton-tipped applicator. Copious irrigation with gentle suctioning followed, and SI proceeded in the usual manner.
After surgery, a small amount of tetracycline ointment was instilled in the operated eye. Patients after surgery, received betamethasone eye drops 6 hourly, chloramphenicol eye drops 4 hourly that after 1 week were tapered. Patients also received oral cephalixin for 1 week. Follow-up visits were scheduled at 1 week, 1, 3, and 6-months postoperative intervals.

During each visit, the same relevant lacrimal function tests were repeated and failures were recorded. In documented failed cases, DCR was offered if the patient’s symptoms could not be managed with nonsurgical managements.

The silicone was left in place for 3 months. Any complication during this time was recorded and managed appropriately. After completion of the study and broken the masking code, all records were reviewed and analyzed. Statistical evaluations included means analysis with the one-way analysis of variance test and comparisons between groups with the Student-Newman-Keuls test. Success rates were analyzed by two-tailed chi-square test. A p value less than 0.05 was regarded as significant.

**Results**

Eighty-eight eyes from 82 patients were included in our study, including; 28 male, 54 female, and mean age 30.51, SD=7.33 years. 48 eyes were right eye and 40 eyes were left eye. Follow-up ranged from 6-23 months (mean; 8 months).

Characteristics of patients in this study are outlined in Table 1. There was no statistically significant difference in age between 2 groups (P=0.94). The operation was classified as successful by absence of epiphora or discharge, patent NLD in irrigation test, and the patient to be symptom free 6 months after removal of silicone. 25 (56.8%) eye in the study group (taking MMC) remained totally symptom free, whereas 19 (43.1%) in this group needed DCR. In the placebo group 19 (43.1%) of 44 eyes remained totally symptom free whereas 25 (56.8%) eyes underwent DCR eventually.

The number of subsequent surgeries was used as one measure of success. Of the MMC group 19 of 44 eyes or 43.1% required further surgery, whereas 25 of 44 eyes, or 56.8% in the placebo group. This difference was not statistically significant (P>0.05).

In patients with only simple epiphora, the success rate was 51.7% in the SI group, and 75.9% in the study group (MMC+SI), with P value of 0.56. In patients who had chronic dacryocystitis with discharge, rate of success was low (24.1%) in both groups without statistical significance difference (P=0.666).

Duration of symptoms prior to procedure in patients that had only epiphora without discharge well correlated with success rate, so that in control group, patients with less than 6 months of duration of symptoms had significantly better results (83.3%) than patients with more than 6 months of symptoms (29.4%) (P=0.004). Addition of MMC to SI in patients with simple epiphora and less than 6 months of symptoms did not have additional effect on efficacy of treatment (P=0.825). However in patients with simple epiphora and more than 6 months of symptoms, success rate in placebo group and SI+MMC group was 29.4% and 71.4%, respectively (P=0.02) (Table 2).

Intraoperative complications were infrequent; mild hemorrhage from punctum during SI in two patients and mild to moderate nasal hemorrhage in nine patients that were controlled without nasal packing.

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of eyes</th>
<th>Treatment</th>
<th>No. of eye with successful outcome*</th>
<th>Male/Female</th>
<th>Age (mean±SD)</th>
<th>OD/OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>SI</td>
<td>19 (43.1%)</td>
<td>13/28</td>
<td>28.1±13.33</td>
<td>23/21</td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>SI + 0.2 mg/ml MMC</td>
<td>25 (56.8%)</td>
<td>15/26</td>
<td>30.52±11.42</td>
<td>20/24</td>
</tr>
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</table>

* Chi-square=0.946, P=0.331
SI: silicone intubation, MMC: mitomycin-C, SD: standard deviation
Postoperative complications were uncommon, and we observed only a pyogenic granuloma near the punctum in one patient that was treated with excision. No complications such as delayed wound healing, abnormal nasal bleeding, mucosal necrosis, infection, or atrophic rhinitis were noted in the patients treated with MMC. All patients who eventually underwent DCR had a successful outcome (100% success rate) without any complication.

**Table 2.** Success rates in the subgroup of simple epiphora (N=58)

<table>
<thead>
<tr>
<th>Duration of symptoms</th>
<th>Success rates</th>
<th>P value</th>
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<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
</tr>
<tr>
<td>&lt;6 months</td>
<td>10/12 (83.3%)</td>
<td>12/15 (80%)</td>
</tr>
<tr>
<td>&gt;6 months</td>
<td>5/17 (29.4%)</td>
<td>10/14 (71.4%)</td>
</tr>
<tr>
<td>P value</td>
<td>0.004</td>
<td>0.59</td>
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</table>

**Discussion**

SI is indicated in the treatment of congenital NLD obstruction and acquired NLD obstruction, with a success rate ranging from 63% to 100%. Success rate of this procedure will decrease according to severity of obstruction and complication during procedure. For this reason DCR is often indicated in patients mainly with a post-sac obstruction, with acute or chronic dacryocystitis, and frequently in those patients whom an SI has proven difficult or has failed already. Although this procedure has higher success rate, it is rather extensive procedure compared with SI. First report of evaluation of efficacy of SI with MMC instead of a DCR was by Liu and Bosley. In present study the authors sought to determine scientifically if MMC application is indeed beneficial in selected patients.

MMC, derived from Streptomyces caespioitus, is an antibiotic-antineoplastic agent that decreases fibroblast collagen synthesis by inhibiting the synthesis of DNA, cellular RNA, and protein. Zilelioglu et al applied MMC intraoperatively in endoscopic transnasal DCR. Histopathologic examinations showed attenuated epithelium with intracytoplasmic vacuoles and subepithelial connective tissue that was loose and hypocellular. They concluded that intraoperative application of MMC favorably affects the wound healing process at the osteotomy site and may enhance the success of surgery. Kao et al applied MMC intraoperatively in external DCR (EXT-DCR) and compared the results with simple EXT-DCR. The success rate in the MMC group was 100% versus 87.5% in the control group. Adhesions between the ostium and nasal septum were found in 25% of patients in the control group, but there was no adhesion in patients of the MMC group. Yeatts and Neves used 0.3 mg/ml MMC intraoperatively in eight repeat dacryocystorhinostomy; all patients remained asymptomatic and maintained anatomic patency. Considering favorable results of MMC in pterygium excision, trabeculectomy, EXT-DCRs, and SI we carried out a randomized, prospective study using MMC during SI at concentrations of 0.2 mg/ml to evaluate its effects.

Many complications have been reported in association with the use of MMC in pterygium and glaucoma surgery. Severe secondary glaucoma, corneal perforation, corectopia, cataract, and scleral calcification were reported with pterygium surgery. Hypotony-related maculopathy, infection, and endophthalmitis complicated glaucoma surgery, and punctual and canalicular fibrosis and stenosis complicated ocular surface neoplasia treatment. No complications from MMC occurred in reports by Liu and Bosley, You and Fang, and Liao et al. Application of MMC in NLD appears to be safe, but a longer follow-up period must be assessed before a definite conclusion can be made.

The optimal dosage and exposure time of this drug are still controversial. Kao et al applied 0.2 mg/ml MMC for 30 minutes and Yeatts
and Neves\textsuperscript{17} used 0.3 mg/ml MMC for 3 minutes, with favorable results. Ugurbas et al\textsuperscript{24} used 0.5 mg/ml MMC for 2.5 minutes with good histopathologic effects. You and Fang\textsuperscript{15} reported application of 0.2 mg/ml MMC and 0.5 mg/ml MMC for the same time of application (5 minutes) that yielded success rates of 100% and 94%, respectively, without any complication. Liu and Bosley\textsuperscript{11} used 0.2 mg/ml MMC without any complication. Randomized studies involving variable dosing schemes and long-term follow-up visits would help to elucidate the optimum drug regimen.

SI of the NLD in adults has a success rate ranging from 22% to 83%.\textsuperscript{6,8,10,21,25,26} Liu and Bosley\textsuperscript{11} performed SI with MMC for complete NLD obstruction in adults and found a 53% success rate with a mean follow-up of 18 months. Angrist and Dortzbach found a 22.2% success rate for complete NLD obstruction and 77.8% for incomplete NLD obstruction following SI.\textsuperscript{27} Kashkouli et al\textsuperscript{28} compared balloon dacryocystoplasty and SI with SI alone in adults with incomplete NLD obstruction and showed that success rate of endoscopic dacryocystoplasty-SI had no statistically significant difference with SI alone in treatment of incomplete NLD obstruction in adults. SI may cause complications such as peripunctal granulation, chronic infection, and canalicular laceration, stent prolapse, and discomfort.\textsuperscript{29}

We divided the patients in our study into two subgroups by symptoms: those who had simple epiphora and those who had chronic dacryocystitis with purulent discharge. The success rates in the patients that had chronic dacryocystitis was lower (23%) compared to patients that had only epiphora (63.7%). In the patients with dacryocystitis, application of MMC did not change our success rate. This means that patients with chronic dacryocystitis would not respond to SI with or without MMC and therefore in these patients DCR is the treatment of choice.

Evaluation of the patients based on the duration of the symptoms showed that in the patients that had only simple epiphora with less than 6 months duration, addition of MMC to SI, had no additional effect on efficacy of treatment. Thus in patients with less than 6 months of symptoms, it is not necessary to apply MMC and SI alone is sufficient with success rate of 83.3%. However in patients with simple epiphora and more than 6 months duration, success rate in SI group and SI+MMC group was 29.4% and 71.4%, respectively. Thus MMC with SI can be used as a good and effective procedure in patients with simple epiphora and symptoms of more than 6 months and causes to increase success rate from 29.4% in SI alone to 71.4% in SI+MMC.

**Conclusion**

In summary, the results of our double-blind, randomized, prospective study showed that SI with or without MMC is disappointing in patients with chronic dacryocystitis. In patients with simple epiphora of less than 6 months of duration, SI alone would be effective in 83% of patients. However in the same group, MMC application during SI does not appear to have additional benefit over SI alone. In patients with epiphora and more than 6 months duration, the application of MMC during SI would result in better efficacy compared to SI alone. Our study replicates the results of previous studies\textsuperscript{11} which showed efficacy of SI alone and the fact that it could effectively substitute for a more extensive procedure such as DCR in patients with simple epiphora, particularly in whom that their symptoms have been newly developed. In longer duration of symptoms of epiphora, application of MMC would increase success rate significantly.

We recommend SI in patients with NLD obstruction and simple epiphora and no discharge when the eventual cosmetic outcome is important for them; SI alone is sufficient when the duration of symptoms is less than 6 months; SI with application of MMC is a better choice in patients with more than 6 months duration of symptoms. We do not recommend these procedures in patients with chronic dacryocystitis and discharge. We also propose that a larger prospective study be conducted to more definitely evaluate the long term outcome.
References