Efficacy of mitomycin-c on success of primary external DCR surgery

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Abstract

Purpose: to evaluate effectiveness of mitomycin-C (MMC) application intraoperatively in cases of primary external dacryocystorhinostomy (EXT-DCR).

Materials and Methods: a total of 96 patients with primary acquired nasolacrimal duct obstruction (PANLDO) were included in a prospective, double-masked, randomized, controlled trial. 50% of patients underwent conventional DCR and 50% underwent intraoperative MMC (0.2mg/ml) application for 5 minutes in the standard DCR procedure. Patients were regularly followed-up. Final outcome at one year of follow-up was used to define success of the surgery. Both subjective decrease in watering and objective patency on syringing were assessed.

Both the patients and the researchers who were assessing the study outcomes were masked to treatment group.

Results: Mean age (SD) of patient was 43.88 (10.51) years. Success rate achieved with DCR procedure with MMC was 97.92% compared to 91.67% with DCR alone. No local or systemic side effects of MMC were found. The success rate was greater in the MMC group than the control group.

Conclusions: Adjunctive intraoperative MMC application with standard DCR surgery has a higher success rate than standard DCR surgery alone. Further larger, randomized studies are needed to confirm these findings.

Keywords: Dacryocystorhinostomy, Mitomycin C, Nasolacrimal duct obstruction.

Introduction

External dacryocystorhinostomy is the surgical technique used for treatment of nasolacrimal duct obstruction (NLDO). Success rate of dacryocystorhinostomy varies from 88 to 95% (by external approach) and upto 87% by nasal approach.(1) Various causes of failure of surgery include undiagnosed canalicular obstruction, improperly made lacrimal or nasal mucosal flaps, small osteotomy, undiagnosed nasal pathology, excessive fibrosis and granulation tissue formation invoke nasal and lacrimal mucosa, membranous closure at ostium, canalicular obstruction, infection and clot formation.(2) A very common cause for failure is osteogenesis and fibrogenesis at the osteotomy. To prevent this complication an anti-prolifrative agent can be used. Mitomycin C (MMC), an alkalizing antibiotic, is an antiproliferative agent. It acts by inhibiting DNA synthesis and interferes with RNA transcription and protein synthesis. Thus MMC acts on cells with high rate mitosis. This study intends to find out effectiveness of intraoperative MMC use in decreasing failure rates in DCR surgery.

Materials and Methods

This is a prospective, interventional study conducted from May 2012 to April 2015 to evaluate outcome of use of intraoperative MMC use in EXT-DCR surgery. Conflict of interest is nil. Informed consent was taken. All the surgeries were performed by same surgeon. Tenets of the declaration of Helsinki were followed. Study protocol was approved by the institutional ethics committee. Patients were randomized into 2 groups, group 1 (EXT-DCR only) and group 2 (EXT-DCR with MMC). Patients with additional pathologies like middle turbinate hypertrophy, deviated nasal septum, nasal polyps, atrophic rhinitis and previous failed DCR were not included in the study. This was done to remove bias due to any additional factors affecting study outcome. Cases below 15 years and above 70 years of age were also excluded out of study. Group 1 underwent standard EXT-DCR surgery and group 2 underwent standard surgery with intraoperative adjunctive MMC 0.2 mg/ml application to the osteotomy site for 5 minutes. Patients with less than 1 year of follow-up after surgery were excluded out of study. Preoperative and postoperative assessment was done using lacrimal syringing, probing and endoscopic nasal examinations. Subjective symptoms of discharge and watering were also assessed.

In both groups, the standard DCR procedure under local anesthesia (3 ml of 2% xylocaine with epinephrine and 2 ml of 0.5% bupivacaine) was followed. A curved incision, confirming with the anterior lacrimal crest was given with 15 no. BP blade. By proper blunt dissection medial palpebral ligament (MPL) and anterior lacrimal crest (ALC) were exposed. MPL was divided and periosteum over ALC was incised. Periosteum and sac were reflected laterally to exposed lacrimal fossa. An osteotomy of approximately 15 mm in diameter was created. Anterior and posterior flaps of nasal and lacrimal mucosa were made. Respective flaps were sutured with 6-0 chromic catgut suture. In group 2, a sponge soaked in 1ml of 0.2 mg/ml of Mitomycin-C was placed at osteotomy site before suturing of flaps.

After 5 minutes, sponge was removed and osteotomy site was washed with plenty of normal saline. Orbicularis muscle was also sutured with the help of 6-0 chromic catgut suture. The skin incision was closed with interrupted 6-0 silk suture. The patients and the researchers were masked to the treatment. Postoperative management included intravenous antibiotics, anti-inflammatory drugs and haemocoagulants. Bandage was opened after one day and gentle syringing was done with 1ml of gentamicin (40mg). Regular follow-ups were done at 1 week, 2 weeks, 4 weeks interval and there after every 2 monthly. Objective and subjective findings were followed up for 1 year.

All cases were evaluated by transcanalicular nasolacrimal irrigation and trans-nasal endoscopic examination. At each visit, the success rate was evaluated objectively based on the patency of drainage system on irrigation and subjectively on degree of epiphora by Munk's score. (Table 1)

Table 1: Munk's score of epiphora

Grade 0	**No epiphora**
Grade 1	Occasional epiphora requiring dabbing < than twice a day
Grade 2	Epiphora requiring dabbing two to four times per day
Grade 3	Epiphora requiring dabbing 5–10 times per day
Grade 4	Epiphora requiring dabbing more than 10 times per day
Grade 5	Constant tearing

Table 2: Subjective improvement in epiphora

Outcome (Munk's score)	**Group 1 (DCR) N=48 (%)**	**Group 2 (DCR with MMC) N=48 (%)**
Poor outcome (4-5)	4 (08.33%)	1 (02.08%
Fair outcome (2-3)	10 (20.83%)	4 (08.33%)
Good outcome (0-1)	34 (70.83%)	43 (89.58%)

Table 3: Patency on syringing

Outcome (patency)	**Group 1 (DCR) N=48 (%)**	**Group 2 (DCR with MMC) N=48 (%)**
poor (regurgitation of fluid)	4 (08.33%)	1 (02.08%
Fair (partially patent)	10 (20.83%)	4 (08.33%)
Good (patent)	34 (70.3%)	43 (08.33%)

Results

A total of 96 patients (eyes) with chronic dacryocystitis were included in the study in a three year duration. Other cases not fitting inclusion criteria were excluded out of study. Among 96 patients, 34 were males and 62 were females. Mean age (SD) of patient was 43.88 (10.51) years. 70.83% of the cases were from rural area while 29.17% cases were from urban area.

Success achieved in the study was graded as 'good', 'fair' and 'poor (failure)' based on outcome. Outcome was assessed objectively, by syringing & subjectively, by Munk's scoring system at the end of 12 months. Good outcome was considered in cases where fistulous opening was freely patent and patients had subjective epiphora of Munk's score 0 to 1. Fair outcome was labelled when passage was patent on syringing but with some resistance to flow and patient had Munk's score 2 to 3. Poor outcome was when passage was not patent on syringing and patient's epiphora scored 4 to 5. (Table 1)

Out of 48 patients in group 1, 4 cases had poor outcome and 10 cases had fair outcome. Out of 48 patients in group 2, 1 patient had poor outcome while 4 patients had fair outcome. (Table 2, 3) All the cases having poor outcome had non-patency by 16 weeks from time of surgery. One case in 3rd week, another 2 in 12th week and 2 more in 16th week. In group 2, success rate based on subjective improvement in epiphora and patency on syringing was 97.92% (n=47) compared to 91.67% (n=44) in group1 (p=0.3616, not statistically significant).

Symptom free eyes were 70.83% (n=34) in group 1 and 89.58% (n=43) in group 2 (p=0.0386, statistically significant). In group 1, 20.83% (n=10) eyes had improvement in symptoms but not complete resolution of symptoms compared to 8.33% (n=4) eyes in group 2. Significantly fewer eyes in group 2 were found symptomatic 10.42% (n=5) compared to 29.17 (n=14) in group 1 (p=0.0386, statistically significant). The success rate was greater in the MMC group than the control group. We didn't found any local or systemic side effects of MMC. No other complication other than non patency in above mentioned cases were found.

Discussion

In this study, female to male ratio was 1.8:1. High predilection of NLDO for females has been reported by many workers. Meller and coworkers suggested that higher involvement in females was due to narrower lumen of bony canal i.e. nasolacrimal canal while Heinonen associated it with nasal index.[3,4] An endocrine etiology has also been suggested by G. Pico.[5] However, no specific reason for the same has been reported in the available literature.

In the study incidence of dacryocystitis has been found more in rural population (61%). This can be attributed to poor hygiene.

Discharge was purulent in 23.33%, mucopurulent in 66.66% and mucoid in 10% cases. This seemed to be directly proportional to duration of existence of dacryocystitis and hygiene. 50% patients complained of swelling at the lacrimal sac area.

Ugurbas et al studied the histopathologic effects of MMC on trans-nasal DCR.[6] Light and electron microscopy found attenuated epithelium and looser, hypocellular subepithelial connective tissue in the MMC specimens.

This finding gives histopathologic evidence of the procedure. MMC was found to be effective in decreasing the density and cellularity of mucosa, thus decreasing failure rates of DCR surgery. Usefulness of MMC in DCR surgery has been evaluated by many researchers. Currently, there are no definite guidelines on dose and duration of MMC application in DCR surgery. Ali et al demonstrated 0.2 mg/ml of MMC for 3 min to be effective in reducing fibrosis without causing much apoptosis.[7] In the present study, higher overall success (97.92% in MMC with DCR compared to 91.67% in conventional DCR) was achieved by MMC use and quality of results was also better in same group (89.58% with MMC-DCR and 70.83% with DCR alone). This suggests MMC application has a definite advantage. A meta-analysis by Qian et al reported increased patency rate with MMC in both external and endonasal DCR.[8] Das et al in 2016 reported 92% success rate in a case series on 150 patients.[9] A success rate of 96.67% with DCR-MMC surgery compared to 80% with conventional DCR was noted by Puzari et al.[10] Kao SCS et al (1997)observed effect of intraoperative 0.2 mg/ml MMC application for 30 minutes on size of ostium after DCR and found statistically significant difference in ostium size in two groups after 6 months from day of surgery.[11] They have also reported in an another study, non-patency rate of 2.5% in MMC group compared to 11.4% in conventional group.[12] You et al concluded that intra-operative MMC in DCR is a safe and effective adjuvant.[13] Deka et al from a study on effect of MMC on ostium size concluded that MMC use leads to larger ostium size throughout the postoperative period.[14] Zilelioglu et al and Yildirim et al didn't find statistically significant difference on using MMC in endoscopic DCR.[15,16] In our study, differences in number of asymptomatic eyes and freely patent system in two groups was statistically significant but overall success rate was not statistically different.

Maximum time to failure was 16 weeks in present study. In cases with failure, dacryocystography showed collection of radio-opaque dye in the osteotomy area. During repeat surgery in 4 cases intense fibrosis at the osteotomy site was found.

Conclusion

Adjuvant intraoperative use of MMC with standard EXT-DCR has significantly higher success rate compared to standard surgery without MMC application. By maintaining adequate and patent ostium it deals with one of the main causes of failure in cases of DCR. The differences in success rate didn't reach statistical significance, however differences in symptomatology rate did attain statistical significance. This might be due to small sample size. We conclude that further research is needed to define use of MMC and extent of benefit gained in primary external DCR.

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