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Clinical assessment of effectiveness of mitomycin c in endoscopic dacryocystorhinostomy

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Abstract
Many studies have been done using Mitomycin-C as antimetabolites. However the results are variable. Mitomycin-C is an alkylating agent derived from *Streptomyces caespitosus*. Few studies regarding the efficacy of this drug have been undertaken and further studies are needed to determine and confirm the efficacy of this drug. The present study was conducted to evaluate the success rate and to compare the results of endoscopic DCR with and without intraoperative Mitomycin-C.
The present study was planned in the Department of ENT in NMCH Patna from July 2018 to Dec 2018.The 40 patients presented with symptoms and signs suggestive of chronic dacryocystitis secondary to distal nasolacrimal duct blockage were enrolled in the present study.
The information generated from the present study concludes that endoscopic endonasal dacryocystorhinostomy is the surgery of choice for primary acquired nasolacrimal duct obstruction. Intraoperative mitomycin C prevents narrowing of ostium. Topical mitomycin C is safer with no local adverse effects. Use of adjuvant mitomycin C enhances the success rate of surgery with less chances of recurrence.

Keywords: mitomycin-C, endoscopic dacryocystorhinostomy, dacryocystorhinostomy (DCR)

Introduction
Dacryocystorhinostomy (DCR) surgery is a procedure that aims to eliminate fluid and mucus retention within the lacrimal sac, and to increase tear drainage for relief of epiphora (water running down the face). A DCR procedure involves removal of bone adjacent to the nasolacrimal sac and incorporating the lacrimal sac with the lateral nasal mucosa in order to bypass the nasolacrimal duct obstruction. This allows tears to drain directly into the nasal cavity from the canaliculi via a new low-resistance pathway.
Nasolacrimal duct obstruction (NLDO) can result in a watery eye, due to obstruction of the outflow of tears. Nasolacrimal duct obstruction occurs as a congenital or acquired disease. Acquired causes can be numerous. The obstruction of the nasolacrimal excretory system may occur in the proximal puncta, canaliculi, common canaliculus, or more distally within the lacrimal sac or nasolacrimal duct. Acquired NLDO may develop for a variety of reasons, including secondary to facial trauma, chronic environmental allergies, toxicity from chemotherapeutic drugs or topical medications, neoplasms, long-standing sinus disease, or following sinonasal surgery. A detailed history is crucial to distinguishing NLDO as the cause of tearing, as opposed to reflexive tearing from other causes. A complete patient history should include assessment of symptoms, daily functional status, pertinent medical conditions, medications used (including sinus decongestants and nasal sprays, topical eye drops such as phospholine iodide), and other risk factors (e.g. facial or nasal trauma, sinus disease, environmental allergies, systemic chemotherapeutic drugs such as taxotere, history of sinus or nasal surgery, periorbital radiation) [1].
The clinical diagnosis of nasolacrimal duct obstruction requiring DCR is made by the patient history, in conjunction with an elevated tear meniscus and demonstration of lacrimal outflow obstruction on probing and irrigation. A delayed dye disappearance test can be a good indicatory of lacrimal obstruction in the pediatric population.
The primary benefit of the endonasal, or internal, approach is the lack of skin scarring. The nasal mucosa and middle turbinate are first decongested for vasoconstriction and hemostasis. Using a nasal endoscope for visualization, the lateral nasal mucosa adjacent to the lacrimal sac is then incised vertically and elevated. The sac location is typically located anterior to the anterior aspect of the middle turbinate along the nasal wall. A fiberoptic endoilluminator, as used in vitreoretinal surgery, may be inserted through the canaliculi into the sac in order to help transilluminate the lacrimal bone medial to the lacrimal sac if needed.
Full exposure of the bone adjacent to the lacrimal sac is needed. Wide elevation of the nasal mucosa is performed with Freer elevators, and the mucosa removed with endoscopic forceps. The lacrimal bone is next removed with a high-speed drill, Kerrison rongeurs, or pituitary rongeurs. Lasers have also been used as well [2, 3]. The final bony ostium should be approximately 8mm in height and include adequate clearance of the common canaliculus internal ostium and the inferior sac to avoid persistent accumulation in the inferior sac (lacrimal sump). After bone removal, the lacrimal sac mucosa is infiltrated with local anesthetic for vasoconstriction, incised, and the medial sac mucosa removed with forceps. Adequate lacrimal sac mucosal removal is confirmed by free flow of saline or fluorescein from the canaliculi through the nasal ostium, or direct visualization of the common internal punctum with the endoscope. Bicanalicular silicone intubation may also be placed as in the external DCR approach, and removed postoperatively in the office. Mitomycin C, an antimetabolite, may judiciously be applied to the intranasal ostium to modulate fibrosis [4].
The endonasal DCR is contraindicated for patients with a suspected lacrimal system neoplasm, or lacrimal sac

diverticulae, lacrimal system stones, common canalicular stenosis, and severe midfacial trauma.

Following surgery, the patient is discharged home if stable and instructed to rest for one week, without heavy lifting, exercise, or strenuous activity that may induce bleeding. Hot drinks and food should be avoided for the first 12-24 hours postoperatively in order to decrease the risk of epistaxis caused by heat-induced nasal vasodilation. Ice/cold compresses are placed on the incision site for 48 hours while awake to minimize swelling and bruising. The patient's head should remain elevated at all times at a 45 degree angle and the patient instructed to avoid nose blowing for one week to decrease the risk of haemorrhage. Skin sutures are removed one week postoperatively if nonabsorbable sutures were used, and the silicone tube is removed typically at 4-8 weeks after surgery.

Scarring during the healing process can cause this channel to close and the operation to fail with a rise in pressure. Mitomycin C is a powerful agent which prevents scarring by inhibiting the multiplication of cells which produce scar tissue. This review asks whether there is evidence that its use during the initial stages of surgery to prevent the excessive conjunctival scarring reduces the risk of failure of the operation. Three types of patient were included: those at high risk of failure because of previous failed surgery or other complications, those having combined cataract and glaucoma surgery and those having primary trabeculectomy - an operation for the first time for their glaucoma. The review found evidence that Mitomycin C reduces the risk of surgical failure in both high risk and primary surgery but no evidence on combined cataract and glaucoma surgery. But the risk of adverse effects including an increased risk of cataracts (not in the combined group) was also noted. There were only a few studies on each category of patients and most were of only poor or moderate quality [5].

Many studies have been done using Mitomycin-C as antimetabolites. However the results are variable. Mitomycin-C is an alkylating agent derived from *Streptomyces caespitosus*. Few studies regarding the efficacy of this drug have been undertaken and further studies are needed to determine and confirm the efficacy of this drug. The present study was conducted to evaluate the success rate and to compare the results of endoscopic DCR with and without intraoperative Mitomycin-C.

Methodology

The present study was planned in the Department of ENT in NMCH Patna from July 2018 to Dec 2018. The 40 patients presented with symptoms and signs suggestive of chronic dacryocystitis secondary to distal nasolacrimal duct blockage were enrolled in the present study.

The initial evaluation of the degree and site of obstruction was evaluated by lacrimal sac syringing with saline. Reflux of fluid through the opposite punctum indicated distal nasolacrimal duct obstruction i.e., the obstruction was in the or beyond the common canaliculus. Reflux from the same punctum indicated proximal obstruction. If the fluid passed into the nose freely with no reflux into the eye, the lacrimal system was labelled as patent not requiring surgery. Thereafter probing was performed using the Bowman's probe for the cases where there was suspicion of distal obstruction.

Group I patients underwent endoscopic dacryocystorhinostomy followed by application of Mitomycin-C (0.5mg/ml solution of Mitomycin-C applied at stoma site for 5 minutes). Group II patients underwent endoscopic dacryocystorhinostomy without application of Mitomycin-C.

A surgical sponge was embedded in 0.5 mg/ml solution of Mitomycin C and applied to the mucosal border of the osteotomy site for 5 minutes under endoscopic visualisation. Maximum care was taken in order to have all circumferential mucosa in contact with the sponge. After removal of the sponge, the area was irrigated thoroughly with saline solution. A change in the colour of the nasal mucosa from red to white-grey was visible immediately after application. Commercial Nasal haemostatic packs were given for 24 hours.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion Criteria

patients with nasolacrimal duct blockage willing to undergo endoscopic dacryocystorhinostomy; patients above twelve years of age.

Exclusion Criteria

(a) Marked deviated nasal septum to same side, (b) Features of Chronic rhinosinusitis, (c) Nasal tumours, (d) History of previous DCR, (e) Cases diagnosed with canalicular block.

Results & Discussion

Dacryocystorhinostomy (DCR) is the procedure of choice in patients with epiphora due to primary acquired nasolacrimal duct obstruction. Caldwell and Toti were the pioneers who first described endonasal and external DCR, respectively [6, 7]. Subsequently, the evolution of sugcls, the advent of fiber-optic endoscopes, better anesthesia techniques and the adjunct use of anti-metabolites intraoperatively and postoperatively by some; namely mitomycin-C (MMC) have significantly contributed to the advancement of DCR surgery. In experienced hands, DCR is a very successful procedure. The surgery may be performed either externally through a skin incision or endonasally with the help of fiber-optic endoscope. However, both surgical routes have reported failure rates ranging from 0% to 18%, due to blockage of osteotomy due to granulation tissue, scarring and formation of adhesions and synechiae in the nasal cavity [8, 9]. During the postoperative healing process, scarring can further decrease the ostium size [10]. Therefore, the key to increasing the longevity of the success of a DCR, obviously lies in maintaining the patency of the ostium. The use of anti-metabolites, which inhibits circumosteal fibrous tissue growth and scarring is hence desirable.

Table 1: Postoperative complications wise distribution of cases in group I and group II.

Groups	Group I	Group II
Total Cases	20	20
Post op complication	Observed in	
Fibrosis	2	3
Granulations	0	6
Infection	1	0
Synechiae	3	0

Table 2: Patency of ostium wise distribution of cases in Group I and Group II.

Groups	Group I	Group II
Total Cases	20	20
Patent at	Observed in	
1st week	19	16
3rd weeks	17	15
3rd months	15	14
6th months	15	14

Table 3: Outcome of surgery.

Groups	Group I	Group II
Total Cases	20	20
Success	20	16

Rathore *et al*., in their study to find the role of topical MMC as a postoperative adjunct to endonasal DCR; placed a nasal pack soaked in 1 ml of 0.05% (2 mg in 5 ml of distilled water) MMC after DCR. This was in place for 48 h. In their study, they observed that postoperative retention of nasal packs for 48 h after endonasal DCR did not cause any major side effect. Improvement in clinical symptoms was noted in all patients who had nasal packing with MMC. Postoperatively, the nasal cavity which had been packed with MMC had healthy nasal mucosa during the entire follow-up, as compared to the control group where the saline nasal pack was used, where synechiae were seen in 65.2% of the patients [11].

Zilelioglu *et al*. in one of the earlier studies to comment on the adjunctive use of MMC in endoscopic DCR; used topical 0.5 mg/ml solution of mitomycin intraoperatively and applied the drug for 2.5 min. They demonstrated histopathological evidence that 0.5 mg/ml of MMC for 2.5 min favorably affected wound healing in the osteotomy site. However, this limited series showed no benefit of using MMC intraoperatively as their surgical success rates with and without MMC had success rates of 77.8 and 77.3%, respectively, at a mean follow-up period of 18.2 months [12].

Yildirim *et al*. in a prospective randomized controlled study to study the adjunctive use of MMC in external DCRs noted that while the success rates of the MMC group were higher than those of the control group, the differences did not reach statistical significance [13]. Prasannaraj *et al*. in their results of endoscopic DCR where 38 patients were randomized into either an MMC group (0.2 mg/dL) or a control group, reported a success rate of 82.3% with MMC 85.7% without MMC. Granulations, adhesions, and obliterative sclerosis occurred in a similar number of patients in both groups, and the authors were of the opinion that granulations and adhesions did not have a bearing on the success rate in either group [14].

It is evident from the varying concentrations of MMC that different studies have used that there is no agreement on the issue. It is further unclear as to how researchers arrived at each of these arbitrary concentrations before applying it to practice. Ali *et al*. studied the effect of varying concentrations of MMC and treatment durations on cellular proliferation and viability of the fibroblasts. Nasal mucosa harvested from patients undergoing a DCR was used to establish primary cultures by explant culture method. The cells were then treated with different concentrations of MMC (0.1-0.5 mg/ml) for different time periods (3, 5, and 10 min). Cell viability, cellular proliferation, and the actin cytoskeletons of fibroblasts were studied. The significant findings of this study were that the doubling time of cultured nasal mucosal fibroblasts was found to be approximately 24 h. MMC at 0.4 mg/ml beyond 5 min and 0.5 mg/ml concentration at all time points were lethal and caused extensive cell death when compared with controls. The minimum effective concentration appeared to be 0.2 mg/ml for 3 min as it prevented cell proliferation of the fibroblasts by inducing cell cycle arrest, without causing extensive apoptosis [14].

The most common reason for the failure of this operation is the formation of scar or granulation tissue over the rhinostomy site [15, 16] It is postulated that adjunctive use of MMC over the osteotomy site in EN-DCR surgery could inhibit scarring and granulation tissue formation around the osteotomy site or common canaliculus and enhance the success of EN-DCR surgery. Based on our meta-analyses, it appears that it will be helpful to apply MMC over the osteotomy site to increase the success rate of primary EN-DCR (P=0.045). For revision DCR, the endoscopic approach is especially superior to the external approach. The normal scarring produced after the external incision makes a revision procedure very uncomfortable, and the final aesthetic and functional results are usually poor. In contrast, endoscopic revision DCR is an easy procedure with mainly good results [17, 18]. Moreover, Korkut and associates [19] evaluated the results of primary and revision EN-DCR. They stated that EN-DCR is a safe and effective procedure in revision cases, as well as in primary cases. In the present meta-analysis, only four studies of revision EN-DCR were included. Although the results showed that the success rate was higher in the MMC group than control group (P=0.029), future larger sample size comparative clinical trials are needed to prove it.

The decrease in the size of the healed intranasal ostium after DCR surgery is the result of a normal wound healing response. Recurrent nasolacrimal duct obstruction after primary DCR is mainly due to reclosure of the nasolacrimal stoma and osteotomy site with granulation tissue [20]. One of the attempts to prevent closure of the stoma is local application of Antimetabolites for the inhibition of the wound healing process and the prevention of excessive scar formation in the rhinostomy site.

Conclusion

The information generated from the present study concludes that endoscopic endonasal dacryocystorhinostomy is the surgery of choice for primary acquired nasolacrimal duct obstruction. Intraoperative mitomycin C prevents narrowing of ostium. Topical mitomycin C is safer with no local adverse effects. Use of adjuvant mitomycin C enhances the success rate of surgery with less chances of recurrence.

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