Adjunctive use of mitomycin C on endoscopic lacrimal surgery

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Abstract

***Aims*—Endoscopic endonasal dacryocystorhinostomy (DCR) has some advantages over external DCR as a less invasive method with no skin incisions. But the success rate of the operation has not reached the level of external method. In this study, a wound healing inhibitor mitomycin C was used intraoperatively to prevent the closure of the osteum after the operation.**

***Methods*—Endoscopic endonasal DCR was performed on 40 eyes of 39 patients (26 female, 13 male). Mitomycin C was applied to the ostium in 14 of 23 patients who had undergone primary endoscopic DCR by means of a microdrill and in eight of 17 patients who had a revision endoscopic DCR secondary to a previously failed external DCR.**

***Results*—The postoperative follow up period was 9–27 (mean 18.2) months. The success rate of endoscopic DCR with intraoperative mitomycin C was 77.3%, whereas the success rate of endoscopic DCR without mitomycin C was 77.8%. The statistical analysis did not show a difference between the two groups according to the ostium size and their success rates.**

***Conclusions*—Adjunctive use of a wound healing inhibitor is considered to increase the success rate of endoscopic endonasal DCR. Its intraoperative use seems to be easy and safe. But the study of this limited series shows no benefit in using it.**

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Since its original description by Toti[1] in 1904, external dacryocystorhinostomy (DCR) has been the standard treatment of lacrimal obstruction. Dupuy-Dutemps and Bourguet[2] made some modifications of the technique still in use today. Although internal DCR was described by Caldwell[3] in 1893, the intranasal approach did not become popular until the advent of endoscopy in nasal sinus surgery. The rigid nasal endoscope allowed better visualisation of the nasal cavity and safe intranasal manipulation.

Massero *et al* [4] were first to describe a laser assisted endonasal DCR by means of an argon laser for bone removal. Carbon dioxide,[5] potassium titanyl phosphate (KTP),[5] and holmium YAG[6] lasers have been used in endoscopic lacrimal surgery. A non-laser endoscopic approach for revision of failed external DCR has been described previously.[7] Successful results of endoscopic intranasal DCR were reported with the use of conventional surgical instruments[8] or drills[9] for bone removal. The authors recommended use of additional surgical modalities such as small drills,[6] microrongeur,[10] and radiosurgery[11] for widening the bony window in a recent series of endonasal laser DCR.

Welham and Wulc[12] noted that the scarring of the rhinostomy site was one of the reasons for failed external DCR. Exuberant scarring caused failure in 93% of 15 patients who had undergone secondary surgery in their series. Osteotomy closure by granulation tissue has been reported as the most important reason for failure in endoscopic lacrimal surgery.[10 11]

Mitomycin C, derived from *Streptomyces caespitosus*, is an alkylating antibiotic. It reduces fibroblast collagen synthesis by inhibiting DNA dependent RNA synthesis and can suppress cellular proliferation in any period of the cell cycle. In order to prevent excessive scar formation in glaucoma surgery mitomycin C has been used as adjunctive therapy.[13] Application of mitomycin C in doses of 0.2 mg/ml to 0.5 mg/ml for 5 minutes was effective in subconjunctival fibroblasts.[14 15] Clinicopathological examination of the excised mitomycin blebs also showed the lack of postoperative subconjunctival fibrosis when mitomycin was used in 0.5 mg/ml concentration for 1 to 3 minutes.[16] Jampel concluded that mitomycin C probably did not improve the success of filtration surgery by killing fibroblasts and a 1 minute exposure might be as effective as a 5 minute exposure.[17]

Modulation of the wound healing response to prevent excessive scar formation can also play a major role in endoscopic lacrimal surgery. We used a topical 0.5 mg/ml solution of mitomycin intraoperatively and applied the drug for 2.5 minutes.

In this study, we report the results of 40 endoscopic lacrimal surgery procedures, in which mitomycin C was used as an adjunct in 22 of them.

Patients and methods

Between February 1994 and April 1995 endoscopic intranasal DCR was performed in 40 eyes of 39 patients. There were 26 females and 13 males ranging in age from 19 to 68 years (mean 38.5). Presenting symptoms were epiphora (nine) and chronic dacryocystitis (12). In four cases epiphora was the result of trauma and two of them had undergone a failed external DCR. Seventeen patients (including two cases with trauma aetiology) underwent a revision endoscopic procedure secondary to failed external DCR. Informed consent was obtained from the patients.

All patients underwent a complete ophthalmic and endoscopic nasal examination. They had radiological assessment with dacryocystography and computed tomography was performed in traumatic cases. Only four of the patients with deviation of the nasal septum at the level of middle meatus or anterior end of the inferior turbinate underwent a deviation operation before the procedure.

The operation was performed under local anaesthesia. After appropriate premedication for sedation, 10% lignocaine (Xylocaine) spray was applied through the affected nostril. Nasal packing soaked in 4% cocaine and adrenaline 1:100 000 solution was placed anterior to the middle turbinate for 5 minutes. A 2% lignocaine with 1:100 000 adrenaline solution was injected into the nasal mucosa just superior and anterior to the attachment of the middle turbinate under endoscopic visualisation. Topical anaesthesia to the eye was achieved by an application of two drops of 4% oxybuprocaine solution to the conjunctival sac and nasociliary blockage with 2% lignocaine solution.

The lacrimal puncta on the affected side were dilated and irrigated with a saline solution. A 20 gauge fibreoptic light probe used in vitreoretinal surgery (endoillumnator, Storz instruments, St Louis, MO, USA) was passed through either punctum or canaliculus into the lacrimal sac. In revision surgery, a Bowman lacrimal probe was inserted through either punctum or canaliculus into the lacrimal sac to tent the mucosa of the lateral nasal wall as described by Metson.[18] Then, a circular incision of nasal mucosa around the underlying probe tip was performed with a sickle knife. The mucosal flap was elevated medially and removed with a straight Blakesley forceps. The medial wall of exposed lacrimal sac was grasped with angled Blakesley forceps and removed to give a wide opening.

In primary endoscopic dacryocystorhinostomy a mucosal flap was elevated from the region just anterior to the middle turbinate in the lateral nasal wall. The bone underlying the flap was constituted by anterior lacrimal crest of the maxilla anteriorly and the lacrimal bone posteriorly. It was removed by means of a microdrill (10 000 cycles/minute) used in ear surgery. The bony window was enlarged to a diameter of approximately 7 mm with a gouge and rongeur. Although it was difficult to remove the thick bone of the anterior lacrimal crest, it provided exposure to the lacrimal sac from the anterior aspect as well as the medial part. The medial wall of the lacrimal sac adjacent to bony window was tented by a lacrimal probe and incised with a sickle knife, then removed by angled forceps to create a large mucosal opening. It was easy to see the internal common punctum with the 30 degree endoscope.

After creating the rhinostomy in 22 patients a surgical sponge, which was embedded in 0.5 mg/ml solution of mitomycin C, was applied to the mucosal border of the osteotomy site for 2.5 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 and aspirated with an intranasal aspirator. A change in the colour of the nasal mucosa from red to white-grey was visible immediately after application.

Bicanalicular silicone intubation (Lacrimal intubation set, 5013, Visitec, Warks) was performed in all patients. The stainless steel probes attached to the silicone tubing were retrieved under endoscopic visualisation by means of a retrieval device (Visitec). Both ends of the tubing were knotted together and sutured to the lateral nasal vestibule with a 5.0 Prolene suture.

A systemic oral antibiotic and topical antibiotic drops were administered to the patients in the postoperative period. In addition, nasal spraying with a steroid spray was applied. The nasal packings (if applied) were removed on the second postoperative day. The silicone tubes were removed within 4–6 months (if they were not lost prematurely). Compliance of the patients with tubing and granulation tissue formation at the ostium were the main factors considered for the time of tube removal. We measured the diameter of the bony ostium created and the healed ostium size after the surgery. For this procedure, a Bowman probe No 000 which was marked at 1 mm intervals was used as described by Linberg *et al.*[18]

Results

Patients were followed up for 9 to 27 months (mean 18.2 months). The operation was considered as successful if the patients had no symptoms, and the lacrimal drainage system was proved to be patent by irrigation. The silicone tubes had been taken out at least 6 months before the last postoperative examination.

Of the 40 procedures performed, 17 were secondary to failed external DCR. In eight of these patients mitomycin C was used intraoperatively. Primary endoscopic DCRs were performed in 23 cases, and mitomycin C was used in 14 of them. Primary endoscopic DCR was performed to a patient whose other eye had a revision endoscopic procedure.

All patients underwent endoscopic nasal examination during the last follow up to determine any granulation tissue or synechia formation in nose; their healed intranasal ostium size was also measured.

The success rate in 23 cases who had undergone primary endoscopic intranasal DCR was 78.3%. Eleven of 14 cases (78.5 %) operated with mitomycin C were successful. Revision endoscopic DCR was successful in 13 of 17 cases (76.5%). In this group, intraoperative mitomycin C was used in eight cases and six of them (75.0%) were patent (Table 1). There was no difference between the success rates of primary and revision endoscopic intranasal DCR groups ($p>0.05$, according to Fisher's exact χ^2 test).

Mitomycin C was used in 22 of 40 cases. Silastic tubes were left for a mean of 5.8 months in the mitomycin C group and 5.2

Table 1 Success rates according to the operation type and drug use

Operation	*Mitomycin treated*	*Mitomycin untreated*	*Total*
Primary endoscopic DCR	14	9	23
Success rate	11/14 (78.5%)	7/9 (77.8%)	18/23 (78.3%)
Revision endoscopic DCR	8	9	17
Success rate	6/8 (75.0%)	7/9 (77.8%)	13/17 (76.5%)
Total	22	18	40
Success rate	17/22 (77.3%)	14/18 (77.8%)	31/40 (77.5%)

months in the group operated without mitomycin C. These two groups were compared according to sex, age, type of the procedure (primary or revision), time of the silastic tube removal, and follow up period. There was no statistical difference between them according to Student's *t* test ($p>0.05$). The success rate in the mitomycin C treated group was 77.3% (17/22), whereas in the untreated group it was 77.8% (14/18). These rates did not differ significantly (Fisher's exact χ^2 test, $p>0.05$).

Average ostium size created in the operation was 35.7 mm^2 in the mitomycin C treated group and 35.3 mm^2 in the untreated group. Healed intranasal ostium sizes measured in the follow up examinations were 1.7 mm^2 and 1.5 mm^2 respectively. Ostium sizes created in the operation and measured in the last follow up examination were not significantly different between two groups (according to *t* test, $p>0.05$).

Intraoperative application of mitomycin C has not caused any systemic problems since it is not absorbable from gastrointestinal tract. No nasal or gastrointestinal irritation has been observed during application.

Discussion

Endoscopic endonasal dacryocystorhinostomy has been generally performed by means of a laser. But in recent series microdrills, microronger, and radiosurgery were used in conjunction with the laser for widening the bony window.[10 11] Previous series required the removal of lacrimal bone only whereas recent reports included for the removal of thick bone of maxilla forming anterior lacrimal crest.[11] Success rates were higher in the groups in which additional surgical instruments had been used. This finding was related to the larger ostium created with those instruments.

Linberg *et al* [19] showed that a mean intranasal ostium size of 1.8 mm was enough to be successful in external DCR. This finding favoured endoscopic laser assisted DCR, but the success rate of endoscopic surgery was lower than the conventional method. The lower success rate was most probably due to inability of a direct suturing between nasal mucosa and the mucosa of the lacrimal sac. Since the maintenance of a patent surgical fistula requires an epithelial anastomosis within the fistula and a continuous pressure or flow of fluid,[19] a silicone stent was needed for some time after endoscopic procedures. A significant difference was found between the patients who retained the silicone tube adequately and those who did not.[10]

The decrease in the size of the healed intranasal ostium after surgery is the result of a normal wound healing response. A fistula is created between the anterior chamber and the subconjunctival region for aqueous drainage in glaucoma filtration surgery. The scar tissue which occurred as a result of normal wound healing in subconjunctival tissue causes failure of this fistula. Antimetabolites which can inhibit DNA or RNA replication, cell division, protein synthesis, and fibroblast proliferation have been used as adjunctive therapy to prevent excessive scar formation in glaucoma surgery.[14] Mitomycin C is the most popular antifibrotic agent used intraoperatively. It is highly toxic when used systemically in antitumour therapy. Intraoperative application of mitomycin C in lacrimal surgery is a new indication. When used as a 0.5 mg/ml concentration for 2.5 minutes, intraoperative application of mitomycin C favourably affected the wound healing process.[20] The application period of the drug was shortened for this relatively benign disease. This variation was thought to decrease the possible penetration of drug beyond the surgical borders.

Analysis of Boush *et al*'s[10] series showed that the majority of the surgical failures occurred within 4 months after endoscopic surgery. A similar finding was also seen in Kong *et al*'s study.[11] They reported that the average onset of ostium closure after the primary operation was 6 to 26 weeks (mean 12.7 weeks).[11] Woog *et al* [6] also reported that the average onset of failure was 7.5 weeks postoperatively (2–14 weeks). No patient in this series had osteum closure after 16 postoperative weeks. All of these findings indicated that the critical period was 4–6 months after endoscopic surgery. We left the silastic tubes 4–6 months if they were not prematurely lost. However, antifibrotic mitomycin C was thought to be effective in the inhibition of the wound healing process and the prevention of excessive scar formation in the rhinostomy site.

Closure of the osteotomy site with granulation tissue occurred in nine cases, causing failure of surgery. Granulation tissue formation also occurred in the mitomycin C group. Adjunctive use of mitomycin C has not been found to be effective in this process, yet the results of the mitomycin C group did not show a statistical difference compared with the untreated group.

Our success rate of primary endoscopic DCR by means of a microdrill was 78.3% (18/23).This ratio was compatible with the results of endonasal laser dacryocystorhinostomies after a single attempt. Boush *et al* reported 70% success rate in primary endoscopic procedures, whereas Kong *et al* had 77.2% success in the first operation. In their series, a second operation was performed on failed cases, so that their success rate increased to 80% and 88% respectively. Those success rates were still lower than the conventional method in experienced hands.[21 22]

Metson had a 75% success rate in 12 cases with the same revision endoscopic DCR technique we used for failed external DCR cases.[18] We had a similar success rate (76.5%) in 17 cases. Walland and Rose had 91% success rate in 89 cases in whom they

performed a second external DCR.[23] Welham and Wulc had 85% success in second and 87% in third attempts with the external method.[12] It seems obvious that the endoscopic approach was not superior to the external method, although revision with endoscopic approach was easier to perform in the environment of the altered anatomic structure of the medial canthal region after the previous operation.

The mean ostium size in our series was around 35 mm^2 which was typically achieved with endonasal surgery. Increasing the size of the ostium also increases the duration of operation and patient discomfort. On the other hand, the small size of the rhinostomy despite silicone intubation lowers the success rates compared with the external method.

The success rates of endoscopic endonasal DCR must attain those of external DCR to become an effective alternative. Various methods such as silicone sponge implant, Gelfoam-thrombin stent, and C flex catheters were used to increase the success of dacryocystorhinostomies.[11] Woog *et al* reported that the use of C flex catheters in endoscopic DCR increased their success rate. Boush *et al* described the use of mitomycin C in endoscopic DCR, although those cases were not included in their series. Application of a wound healing inhibitor is a new treatment modality in endoscopic lacrimal surgery. Its intraoperative use seems to be easy and safe, but results of this limited series showed no benefit in the use of the drug.

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