The Efficacy of Application of Mitomycin-C in Endoscopic Endonasal Dacryocystorhinostomy

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Abstract

Design: Prospective study.

Aim of the study: The aim of this study is to evaluate the efficacy of application of Mitomycin-C intraoperatively to the created stoma in endoscopic endonasal dacryocystorhinostomy (DCR) and compare the results with the results of endoscopic endonasal DCR procedure without Mitomycin-C.

Time and place: Study was performed in Al-Sadder medical city in Al-Najaf Governorate during the period from March 2012 to April 2014.

Patients and methods: Sixty seven eyes of 64 patients, there were 46 females and 18 males ranging in age from 5 to 56 years. Patients were randomly divided into 2 groups: group 1 an endonasal endoscopic DCR surgery done without Mitomycin-C application and group 2 in which 0.2 mg/ml Mitomycin-C was applied to created stoma for 5 min.

Results: Mean age for male is 21.7 years and for female 35.29 years. Nasal synecchia was identified in the ipsilateral site of surgery in 5 (15.625%) patients in group 1 and 3 (9.375%) patients in group 2. Two patients (6.25%) in group 1 and one patient (3.125%) in group 2 developed granulation tissue around the stoma and represent as failure operation.

Conclusion: The endoscopic DCR is a relatively safe and effective procedure for treatment of distal lacrimal apparatus obstruction. Endoscopic DCR should be considered in all age group patients and in patients who wish to avoid a facial scar. It is difficult to make a definite evidence-based determination about the relative efficacy of Mitomycin-C application in endonasal endoscopic DCR because there was many studies that show highly successful rate of use of Mitomycin-C and other studies denied this possibility. Antimitotic agents is a new treatment modality in endoscopic lacrimal surgery, its intraoperative use seems to be easy and safe, but in our study and others limited series showed no benefit in the use of the drug.

Keywords: Endoscopic Endonasal Dacryocystorhinostomy (DCR), Mitomycin-C, Nasolacrimal duct obstruction, Epiphora etc.

Introduction

Epiphora (excessive tearing) is a common complaint. For some this is a minor inconvenience but for others it can be extremely troublesome, and a source of social embarrassment as it can alter refraction and mean that the patient has to wipe their eye(s) perpetually. Today’s endoscopic endonasal dacryocystorhinostomy (DCR) is a reliable and effective technique that is comparable to external DCR in outcome measures. The two most common causes of failure in endonasal endoscopic DCR surgery are closure of the surgically created stoma with soft tissue and obstruction at the common canaliculus. 1 DCR surgically bypasses the most distal portion of the lacrimal apparatus, creating a new outflow in the lateral wall of the nasal cavity instead of below the inferior turbinate. Thus, DCR is specifically designed to manage obstructions of the lacrimal sac and duct.2 Antiproliferative agents applied at the created stoma may reduce the fibrosis and hence reduce the failure rate.1 It is difficult to be categorical about any benefit of these agents. There is good theoretical evidence to support their use and in vitro experiments but no clear benefit has been demonstrated.8 Mitomycin-C was firstly developed in 1955 by Hata et al. from Streptomyces caespitosus 13 with half life 8-48 minutes, is an alkylating antibiotic, an antiproliferative agent.7 It reduces fibroblast collagen synthesis by inhibiting DNA dependent RNA synthesis and can suppress cellular proliferation in any period of the cell cycle.6 In order to prevent excessive scar formation in
glaucoma surgery Mitomycin-C has been used as adjunctive therapy. Boush et al was the first to suggest that postoperative fibrosis could further be limited by the application of Mitomycin-C to laser – assisted DCR in 1994.5 At low concentration of 0.2 mg/ml, it inhibits human fibroblast, this property of Mitomycin-C is useful in endoscopic DCR surgery, as it prevents postoperative granuloma formation at surgical stoma. Intraoperative local application of Mitomycin-C is also free from systemic side effect, as there is minimal gastrointestinal tract absorption.11 The drug is available in a vial (10mg/ml). It is further reconstituted with normal saline (25ml) to make 0.4 mg/ml or in (50ml) to make 0.2mg/ml.

Aim of study

Aim of this study is to evaluate the efficacy of application of Mitomycin-C intraoperatively to the created stoma in endoscopic endonasal dacryocystorhinostomy & compared the results with results of endoscopic endonasal dacryocystorhinostomy procedure without Mitomycin-C.

Patients and Methods

Study was performed in Al-Sadder medical city in AL-Najaf Governorate during the period from March 2012 to April 2014. Endoscopic endonasal DCR was performed in 67 eyes of 64 patients. There were 46 females and 18 males ranging in age from 5 to 56 years. Patients were divided randomly into 2 groups: group1 (control group) an endonasal endoscopic DCR surgery done without Mitomycin-C application and group2 in which Mitomycin-C was used during DCR surgery. The surgical procedures in both groups were exactly the same, except that in the patients in the Mitomycin-C group, a piece of surgical cottonoid soaked with 0.2 mg/ml Mitomycin-C was applied to the created stoma for 5 minutes.9 Informed consent of patients those with Mitomycin-C application, have been signed before operation after told them about risk of complication, and side effect of Mitomycin-C.

Surgical intervention was performed under general anesthesia with orotracheal tube. Nasal mucosa decongestion was done by placing a cotton pledges soaked in 0.1% xylometazoline along the lateral nasal wall at the site of DCR prior to and during the surgery. An injection of 2% lidocaine with 1:100,000 epinephrine might be done in some patients into the submucosa just anterior to the attachment of the middle turbinate along the lateral nasal wall and to anterior end of middle turbinate Fig (2). The injection was given under direct visualization with the endoscope.

Mucosal incision

A vertical incision was made on the lateral nasal mucosa using Cottle knife about 10 mm anterior to the axilla of the middle turbinate and maxillary line, from a level few millimeter above the axilla of the middle turbinate (Fig.3). A posteriorly based mucoperiosteal flap was elevated with a suction Freer elevator past the lacrimal bone and just onto the uncinate process(Fig.4). The flap was excised using a through cutting punch forceps or Blackesley forceps.

Bone removal (Fig 6)

The suture line between the lacrimal bone and the frontal process of the maxilla was located with a ball probe. The lacrimal bone at the lateral wall of the nose is easily identified as thin layer of bone just anterior to the uncinate process. The average width of the thin lacrimal bone is 2.5 mm which would allow a 2 mm bony punch forceps to infracture through and engage at the posterior bony edge of the frontal process of the maxilla. Several bites anteriorly and superiorly expose the underlying inferior portion of the lacrimal sac, gentle external pressure was applied on the sac in the region of the medial canthus, causing the sac wall to bulge into the nasal cavity. The exposed sac has a dark red colour and is firmer than nasal mucosa (Fig 5).
A silicon stent attached to metal introducer were passed through the upper and lower canaliculi, a dilatation of the puncti might be needed prior to the insertion, and grasped with a Blacksely forceps(Fig 10), withdrawing from the nasal cavity and cut from the metal introducer. Then in 32 patients in our study, a surgical cottonoid rapped on Jobsen horne, which was soaked with 0.2 mg/ml solution of Mitomycin-C, was applied to the mucosal border of the created stoma for 5 minutes under endoscopic visualization (Fig11). Maximum care was taken in order to have all circumferential mucosa in contact with the piece of surgical cottonoid. After removal of the sponge, the area was irrigated thoroughly with saline solution and aspirated with an intranasal aspirator. The ends of the silicon stent are then tied and trimmed within the nasal cavity (Fig 12). A Merocele sponge was placed in the middle meatus, to be removed 24-48 hour later. A nasal pack was placed for 24 hours.

Sac incision: Metal introducer of the silicon stent is inserted into the inferior canaliculus, (Fig 8) often after dilatation of the corresponding punctum, and into the lacrimal sac tenting it medially. Then surgeon identifies the metal introducer visible within the translucent sac wall. If the metal introducer is not creating a sharp-pointed projection, but instead is causing a more generalized movement of the sac, the metal introducer has not yet emerged from the common canaliculus and requires further manipulation until its point is clearly seen within the sac. This maneuver serves to isolate the medial wall and prevent inadvertent injury to the underlying structures. The sac is incised with a sickle knife or scalpel knife no.15 anterior to the probe (Fig 9), the opening is enlarged to a diameter of 5 mm to 10 mm with a through cutting forceps.

Fig 4: Bone removed by Kerrison punch forceps

Fig 5: Lacrimal sac exposed

Fig 6: Lower punctum dilatation

Fig 7: Lacrimal sac opened by 15 scalpel knife

Fig 8: Silicon stent delivered through newly created stoma

Fig 9: Mitomycin-C application

Fig 10: Silicon stent tied within the nasal cavity
Table 1: Characteristics and statistical results of the cases in our study

<table>
<thead>
<tr>
<th>p-value</th>
<th>Total</th>
<th>group 1 an endonasal endoscopic DCR surgery done without Mitomycin-C application</th>
<th>group 2 an endonasal endoscopic DCR surgery done with Mitomycin-C application</th>
<th>Total no. cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>32</td>
<td>32</td>
<td>64</td>
</tr>
<tr>
<td>0.5</td>
<td>17</td>
<td>9</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>47</td>
<td>23</td>
<td></td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>0.017</td>
<td>5-45 (mean25)</td>
<td>9-45(mean27)</td>
<td>5-41(mean 23)</td>
<td>Age male (year)</td>
</tr>
<tr>
<td>0.45</td>
<td>18-56 (mean37)</td>
<td>20-56(mean38)</td>
<td>18-45(mean31.5)</td>
<td>Age female(year)</td>
</tr>
<tr>
<td>0.3</td>
<td>27</td>
<td>13(41%)</td>
<td>14 (44%)</td>
<td>27</td>
</tr>
<tr>
<td>0.5</td>
<td>34</td>
<td>18 (56%)</td>
<td>16 (50%)</td>
<td>34</td>
</tr>
<tr>
<td>0.0096</td>
<td>3</td>
<td>1 (3 %)</td>
<td>2 (6 %)</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>0.25</td>
<td>2</td>
<td>0</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>0.5</td>
<td>1</td>
<td>0</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2: Postoperative outcome summery in our study

<table>
<thead>
<tr>
<th></th>
<th>group 1 an endonasal endoscopic DCR surgery done without Mitomycin-C application</th>
<th>group 2 an endonasal endoscopic DCR surgery done with Mitomycin-C application</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Major orbital &amp; intracranial complication</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Synecchia</td>
<td>5(15.625%)</td>
<td>3(9.375%)</td>
<td>8(12.5%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Granulation tissue around stoma</td>
<td>2(6.25%)</td>
<td>1(3.125%)</td>
<td>3(4.69%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Persistent epiphora ( failure DCR)</td>
<td>2(6.25%)</td>
<td>1(3.125%)</td>
<td>3(4.69%)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Table 3: Endoscopic visualization of ostium with evaluation of tear drainage after removal of stent and further follow up between 5-25months (mean 14.5 months)

<table>
<thead>
<tr>
<th></th>
<th>group 1 an endonasal endoscopic DCR surgery done without Mitomycin-C application</th>
<th>group 2 an endonasal endoscopic DCR surgery done with Mitomycin-C application</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic visualization of ostium</td>
<td>NO.</td>
<td>%</td>
<td>NO.</td>
<td>%</td>
</tr>
<tr>
<td>Patent</td>
<td>30</td>
<td>93.75</td>
<td>31</td>
<td>96.875</td>
</tr>
<tr>
<td>Blocked (granulation tissue around stoma)</td>
<td>2</td>
<td>6.25</td>
<td>1</td>
<td>3.125</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>100</td>
<td>32</td>
<td>100</td>
</tr>
</tbody>
</table>

Result

Patients details (Table 1)

The objective assessment was done by Endoscopic visualization and evaluation of epiphora relief. The operation was considered to be successful after complete relief of epiphora and endoscopic confirmation of patency of stoma Fig (11).
Endoscopic endonasal DCR has been accepted as a highly successful procedure in dealing with epiphora from nasolacrimal duct obstruction. It is not easy to compare the published success rates of lacrimal surgery because different studies use different criteria of success and varying patient selection. Endoscopic DCR is one of the upcoming surgeries done now days as it is having better outcome than external approach as it avoids any facial scar, facilitates lacrimal pump mechanism by preserving pumping action of orbicularis oculi muscle, simultaneous treatment of nasal pathologies in one setting like DNS and acute dacryocystitis is not a contraindication, immediate mistakes can be revised at surgery and bilateral cases can be performed simultaneously. Various modifications have been done in endoscopic DCR such as application of Mitomycin-C, use of silicone tubing (stent), laser assisted DCR. In our study male to female ratio was 1:2.76. Gülser Zilelioglu et al 6 reported male to female ratio 1:2 and Rekha R. Mudhol et al 9 reported male to female ratio 1:3. A higher proportion of females underwent DCR operation which had been reported in our study is comparable to other studies mention above. Mean age of the whole study groups at the time of surgery was 30.5 years, ranging between 5 years and 56 years. Mean age for male is 21.7 years and for female 35.29 years. There was significant difference in the age between the two groups p-value 0.0017. This was due to presence of three males in our study below 10 years old with comparable to females, all groups age was more than 18 years old.12 In our study, a surgical cottonoid rapped on Jobsen horne, which was soaked with 0.2 mg/ml solution of Mitomycin-C, was applied to the mucosal border of the created stoma for 5 minutes under endoscopic visualization. Thomas Prasannaraj et al 4, Shu L Liao et al 7, Rekha R. Mudhol et al 9, Cem Yildirim et al 10 all used Mitomycin-C in concentration 0.2 mg/ml. Imtiyaz Ahmad et al 3, Gülser Zilelioglu et al 6, Rekha R. Mudhol et al 9, was applied Mitomycin-C to created stoma for 5 min. In our study two patient (6.25%) in group1, and one patient (3.125%) in group2, developed granulation tissue around the stoma that later impeded the drainage of the tears with consequent stenosis of the stoma and represent as failure operation, this might be due to short period of application of Mitomycin-C 5 min (Shu L Liao et al 7 applied Mitomycin-C to created stoma for 30 min with significant 95.5 % success rate) or might be due to low concentration 0.2 mg/ml (Gülser Zilelioglu et al 6 used Mitomycin-C with 0.5 mg/ml concentration). Long duration of stenting with silicon tube may affect the results due to irritation and infection leading to further scarring, but in our study we removed silicon tube in both groups at same time to exclude affect of tube on stoma. In comparable with other studies Thomas Prasannaraj et al 4, Cem Yildirim et al 10, Ghosh S et al 15, Y. Anadolu et al 16, Roozitalab MH et al 17, whose

**Discussion**

According to Fisher Exact Probability Test, we found that there was statistically insignificant difference in the results between the MMC group and control group p-value = 0.5 (p-value >0.05) (Table 3).
used Mitomycin-C in different concentration (0.2 – 0.5 mg/ml) and applied it to created stoma in different time (2-30 min), all reported that the application of Mitomycin-C did not appear to influence the occurrence of granulations, synechiae, or obliterative sclerosis, nor did it alter the success rate significantly. The most frequently encountered complication was nasal synechiae which identified in the ipsilateral site of surgery in 5(15.625%) patients in group1 and 3(9.375%)patients in group2, between septum and middle turbinate, and between the middle turbinate and the lateral nasal wall. We attributed this due to the presence of the silicon tube that might causes irritation, also may be due to septal and middle turbinate trauma during procedure, however in all the eight patients the synechia was released during follow-up visits and epiphora did not recur, Güller Zilelioglu et al 6 reported 9.3% intranasal synechia. Five patients(15,625%) in group1 and four(12.5%) patient in group2 had recurrent epiphora associated with allergy and flue attacks due to their small stomal size (roughly estimated from 1.5 mm to 6 mm by nasal endoscopy) that later have been relieved by conservative medical treatment. Linberg et al14 showed that a mean intranasal ostium size of 1.8 mm was enough to be successful in external DCR.

Conclusion

The endoscopic DCR is a relatively safe and effective procedure for treatment of distal lacrimal apparatus obstruction. Endoscopic DCR should be considered in all age group patients and in patients who wish to avoid a facial scar. Associated nasal pathologies can be corrected at the same time as that of endoscopic DCR. It is difficult to make a definite evidence-based determination about the relative efficacy of Mitomycin-C application in endonasal endoscopic DCR because there was many studies that show highly successful rate of use of Mitomycin-C and other studies denied this possibility. Antimitotic agents is a new treatment modality in endoscopic lacrimal surgery, its intraoperative use seems to be easy and safe, but in our study and others limited series showed no benefit in the use of the drug.

Recommendation

The usage of Mitomycin-C in preventing fibrosis of the stoma had no benefit and needs to be studied further. Regarding silicon stenting, further studies are required to assess the need for it and duration required for its placement.

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