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A randomized placebo controlled trial of Mitomycin - C in surgical outcome of primary endoscopic dacryocystorhinostomy

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Abstract: *Objective:* To compare the patency of the stoma and relief of epiphora after endoscopic dacrocystorjinostomy (EnDCR) surgery with Mitomycin C and Placebo in cases of chronic dacrocystitis secondary to primary post saccal stenosis. *Design:* Randomised placebo controlled trial. *Materials & Methods:* 40 patients (20 cases with Mitomycin - C and 20 cases of Placebo) diagnosed to have chronic dacrocystitis underwent EnDCR. Using single randomised trial, the rhinostomy site was applied with Mitomycin - C 0.2 mg/ml or placebo for 3 minutes by means of a gelfoam and was washed with 10 ml normal saline. Average time taken for the procedure was 40 minutes. Local massage, serial sac syringing was done on the 3rd, 7th & 14th post - operative day and nasal douching were performed during the follow - up period. Endoscopic suction clearance was done weekly for 1 month, then monthly for 6 months to prevent crusting and adhesions. Follow - up examination was done with an endoscope by the same surgeon at the end of 1 week, 1 month and then monthly ranging from 3 months to 18 months. The surgical outcome was evaluated both subjectively and objectively. *Results:* The overall success rate by subjective assessment at the end of 6th month was 95% in Mitomycin C group compared to 80% in the placebo group. But there was no statistical difference between the surgical outcomes on the basis of subjective evaluation (p= 1). Objective endoscopic assessment revealed that the rhinostomy stoma was visible in 16 (80%) patients with Mitomycin C compared to 14 (70%) patients with placebo, but there was no statistical difference between the 2 groups (p = 0.4053). Failure was observed at the end of 6th month in 1 case (5%) with Mitomycin C compared to 2 cases (10%) in the placebo group. *Conclusion:* EnDCR along with Mitomycin C application helps in preventing the closure of rhinostomy stoma and is preferred treatment of choice in case of chronic dacrocystitis with higher safety, success rate and minimal post - operative complications.

Keywords: Endoscopic dacryocystorhinostomy, Mitomycin C, Chronic dacryocystitis, DCR.

Introduction

Search for an alternate to the external dacryocystorhinostomy (DCR) is motivated by the desire to improve endonasal DCR success rate and to add other advantages, such as one stage procedure better compliance by the patient. However failures encountered in Endonasal Dacryocystorhinostomy (EnDCR) are due to closure of the stoma created in the lateral nasal wall due to scar formation during the healing process will decrease or compromise the created surface area of the osteotomy site, leading to surgical failure. Lindberg and Anderson [1] showed that an appropriately large osteotomy made during surgery can narrow down to a final stage of approximately 2 mm because of tissue growth and scarring. Thus if we can reduce fibrous proliferation at the osteotomy site and anastomosis flaps, the success rate of EnDCR could improve. Many methods have been devised to prevent closure of the stoma such as creation of mucosal flaps, intubation of canaliculi lacrimal sac and stoma using silicone tubes, use of alkylating agent such as Mitomycin C.

The aim of EnDCR surgery is not only to establish a free passage between lacrimal sac and the nasal cavity, but also to keep this passage patent. The long term results are good though some failures have been reported most which are commonly attributed to stenosis or closure of rhinostomy. To overcome this

application of 0.2 mg/ml of Mitomycin – C to the rhinostomy opening have been suggested for providing a permanent rhinostomy [1-2].

Mitomycin – C an anticancer agent isolated from Streptomyces caespitasus. It acts a bifunctional or trifunctional alkylating agent. It inhibits DNA synthesis and cross – links DNA to an extent proportional to its content of guanine and cytosine. Its action is most prominent during the late G1 and early S phases of the cell cycle. It is an antiproliferative agent which has the property of suppressing fibrosis and vascular ingrowth [3-4]. The aim of the present study is based on a broad objective to compare the patency of the stoma and relief of epiphora after EnDCR surgery with Mitomycin – C and a Placebo in cases of chronic dacrocystitis secondary to primary post saccal stenosis.

Material and Methods

Institutional ethical clearance obtained and a single blinded randomized clinical trial was conducted on 40 patients (20 cases with Mitomycin – C and 20 cases of Placebo) diagnosed to have chronic dacrocystitis between January 2007 to December 2007 in KLE University's Dr. Prabhakar Kore's Hospital & Medical Research Centre, Belgaum. The case with presaccal block, previous lacrimal trauma, atrophic rhinitis, diabetes mellitus, suspicion of malignancy, revision cases and age less than 12 years were excluded from the study. Patients who required other nasal procedures like septoplasty, release of adhesion and clearance of agger nasi were included in the study.

The diagnosis was made by patient's history – recurrent infections of the lacrimal sac and intermittent or permanent epiphora were the most frequent symptoms. Diagnostic procedures included catheterisation and irrigation of the lacrimal duct. All the cases were operated by a single surgeon and under local anaesthesia. The mucosa of the lateral nasal wall in the region of the maxillary line was infiltrated with 2% lignocaine with adrenaline (1: 100,000). A 1 cm2 incision was made in the lateral nasal wall with the help of sickle knife or 12 no. blade, starting just anterior to the axilla of the middle turbinate. Mucosa was resected using a Freer's elevator. Under endoscopic control, the entire, medial bony covering of the sac was removed using 2 mm Kerrison's punch. A sickle knife was used to open the sac in a cruciate manner. The Kerrison's punch was used to punch the medial wall of the sac. After creation of adequate rhinostomy, using single blinded randomised trial the rhinostomy site was applied with Mitomycin – C 0.2 mg/ml or placebo for 3 minutes by means of gelfoam and was washed with 10 ml normal saline. Nose was packed with medicated ribbon pack for 24 hours. The average time required for surgery was 40 minutes. No stent was used and nasal pack was done at the end of surgery.

Local massage, serial syringing of the sac on the 3rd, 7th and 14th postoperative day and nasal douching were performed during the follow –up period. Short term complications of the procedure like pain, bleeding, vomiting and infection were also evaluated. Endoscopic suction clearance was done weekly for 1 month, then monthly for 6 months to prevent crusting and adhesions. We followed up the cases at the end of 1 week, 1month and then monthly ranging for 3 months to 18 months. Follow – up examination was done under endoscope by the same surgeon. The surgical outcome was evaluated both subjectively and objectively.

Statistical Analysis: Except the age, other parameters in the study are of qualitative nature. Hence student's unpaired "t" test was used to compare the ages of 2 groups and constructing suitable contingency table. Pearson's 2 test was used to find the association between 2 qualitative variables. Medicalc 8.2 statistical software is used in the analysis.

Results

In this study, 40 EnDCR operations were done under single blinded randomized clinical trial (20 cases with Mitomycin C and 20 cases with Placebo). In the present study, 50% patients belonged to the low socioeconomic group, 37.5% were from the middle socioeconomic group while 12.5% belonged to the upper class. In our study, age group ranged from 15 years to 80 years. The mean age was 51.8 years (range 23 to 80 years) in patients with placebo whereas 45.25 years (range 15 to 65 years) in patients with Mitomycin C.

The difference was statistically insignificant (p = 0.2575). 60% cases presented with left-sided disease whereas 40% presented with right-sided disease. Of all cases, condition of the sac was distended in 6 (15%) cases, normal in 30 (75%) cases and cicatrized in 4 (10%) cases. Other procedures like septoplasty was done in 4 cases (1 in placebo group and 3 in Mitomycin C group) prior to beginning EnDCR. Out of 4 cases, 3 cases were endoscopic assisted septoplasties and 1 cases conventional septoplasty. Partial anterior middle turbinate reduction was done in 1 case of placebo group. Uncinectomy was done in 3 cases (1 in placebo group and 2 in Mitomycin C group). Synechiae was released in 1 case of Mitomycin C group. Grade 3 bleeding in the surgical field (brisk bleeding with frequent suction required) [5] was observed in 3 (7.5%) cases and grade 2 bleeding (minimal bleeding with infrequent suction required) in 37 (92.5%) cases. The mean duration of follow-up was 10.34 months (range 6 to 15 months) for patients in the placebo group, whereas it was 11.05 months (range 6 to 18 months) for patients with Mitomycin C.

The outcome of subjective assessment of the surgery at 6th month was as follows. In Mitomycin C group 14 (70%) patients became symptom free, 4 (20%) reported significant improvement, 1 (5%) had slight improvement and 1 (5%) case the condition was the same as before. In the placebo group 12(60%) patients became symptom free, 4 (20%) patients reported significant improvement and 2(10%) cases the condition were the same as before. The overall success rate at 6th month follow up was 90% in the placebo group and 95% in the Mitomycin C group. But there was no statistical significant difference between the surgical outcomes on the basis of subjective evaluation (p = 1).

The data of the objective assessment at 6^{th} month were as follows. Rhinostomy was visible in 14 (70%) patients with placebo and 16 (80%) patients with Mitomycin C. 5 (25%) patients with placebo had some form of granulation tissue at the rhinostomy opening whereas only 2 (10%) patients with Mitomycin C. There was no statistical difference between the 2 groups (p = 0.4053). 5 (25%) patients with placebo and 2 (10%) patients with Mitomycin C had synechiae between nasal septum and anterior end of the mucosal incision on the lateral wall and also between middle turbinate and lateral wall of the nose. Spontaneous methylene blue flow was noticed in 15 (75%) cases with placebo and in 17 (85%) cases with Mitomycin C.

Flow present on pressing the sac was observed in 3 (15%) patients with placebo and in 2 (10%) patients with Mitomycin C group. There was no flow in 3 (10%) patients with placebo and in 1 (5%) patient with Mitomycin C. Failure observed at 6^{th} month was in 2 (10%) cases in the placebo group and 1 (5%) case with Mitomycin C. Rhinostomy had been closed by scarring and fibrosis.

Discussion

In our study, we found that dacrocystitis was more common in the lower socioeconomic class (50%), followed by middle socioeconomic class (37.5). Our data correlated well with studies of Duke Elder [6] which highlights that dacrocystitis is common among lower socio economic group due to poor hygiene. Patient's negligence and drug resistance are the other contributing factors to the chronicity of the disease.

In the present study, the female to male ratio is 27:13. The difference of gender in between the 2 groups was statistically insignificant (p = 0.2575). In a study conducted by Manfred Weidenbecher et al [7], the female to male ratio was 3:2. Similarly in another study conducted by Hartikainen et al [8] showed a ratio of 23:9. This female preponderance can be explained due to long duration of exposure to smoke in kitchen, dust in the external environment and use of cosmetics like kajal [9].

In our study, left sided disease (60%) was more common than right sided disease (40%). According to Arist [10], found that the left side was more involved than the right due to greater angle formed by the nasolacrimal duct and lacrimal fossa on the right side. Other explanation is that most people are right handed, hence their left hand is free and used for cleaning the eye or mopping of tears that increases the chance of infection in the left eye. Another possibility could be congenital, anatomical narrowing of NLD on the left side. In 39 (97.5%) cases we noticed sac in the

normal position. Out of 4 cases of cicatrized, 1 case we had difficulty in locating the sac and was superiorly placed. We observed failure in this case. During the operation, minimal bleeding with infrequent suction required in the surgical field (grade 2) was in 37 (92.5%) cases and brisk bleeding (grade 3) in 3 (7.5%) cases. In post operative follow-up cases 2 cases (5%) had pain and cellulitis of the medial canthal region was developed on the 3rd post operative day and it resolved with parenteral antibiotics. The success rate in this study was 95% in the Mitomycin C group and 80% in the placebo group. This success rate in Mitomycin C group was clinically significant but statistically not significant (p = 1). The reported success rates of EnDCR vary between 83% and 96% [7,9,11-21] (Table 1).

Author	Procedure	Result (%)	Comments
Weidenbecher et al [7] (1994)	EnDCR with stent	95	Traumatic cases had little less favourable result.
Singh et al [9] (2004)	EnDCR without stent	96	Successful in atrophic rhinitis & other nasal conditions.
Onerci et al [11] (2000)	Gr-1: Experienced surgeon Gr-2: Inexperienced surgeon	94.5 58	Success is defined as relief of symptoms & lacrimal irrigation.
Cokkesser et al [12] (2000)	Gr-1: Ext DCR Gr-2: En DCR without stent	89.5 88.2	Success defined as resolution of epiphora.
Fayet B et al [13] (2002)	EnDCR with stent	86	Anterior resection of uncinate in all cases and partial resection of middle turbinate optional.
Wormald et al [14] (2002)	Powered EnDCR with stent	95.7	Used drill & other instruments
Young et al [15] (1998)	Lacrimal sac/ duct block Common canalicular block Canalicular block	95 86 57	All patients were stented. Outcome measured according to degree of symptom relief.
Unlu et al [16] (2002)	Gr-1: EnDCR with silicon intubation Gr-2: EnDCR without silicon intubation	85.7 81.3	Evaluation included subjective & objective tools. No randomisation.
Seppa et al [17] (1994)	En CO_2-Nd: YAG laser DCR	83	Additional use of fiberoptic illuminator of sac & microscope.
Ibrahim et al [18] (2001)	Endoscopic guided trephination(Hesham DCR)	83	Endoscopic insertion of large lacrimal maintainer.
Yung et al [19] (1998)	Inferior EnDCR with stent	90	Quickert tubes are used.
Maier et al [20] (2000)	EnDCR with stent	90	Dacryo endoscope & microdrill.
Wormald et al [21] (2006)	Assessment of DCR ostium after Powered EnDCR.	94	DCR ostium shrinks a small but significant amount in the first 4 weeks after surgery. Thereafter the ostium size appears to be stable.

Table-2: Clinical Studies evaluating the efficacy of Mitomycin C in endoscopic DCR			
Study	**Procedure with MMC**	**Success (%)**	**Comments**
Zileioglu et al [4] (1998)	Gr-1: EnDCR with MMC Gr-2: EnDCR without MMC	77.3 77.8	Showed not significant
Selig et al [22] (2000)	EnDCR with MMC application	87.5	Small sample size & did not have any control.
Liao et al [23] (2000)	Gr-1: EnDCR with MMC Gr-2: EnDCR without MMC	95.5 70.5	Strongly recommended its use.
Liu et al [24] (2003)	Gr-1: EnDCR with MMC Gr-2: EnDCR without MMC	77.3 77.8	No beneficial effects of MMC & hence not recommended.

These results were similar to our success rates. There are a few randomised comparative studies of the surgical results of EnDCR with and without Mitomycin C. However, few clinical studies evaluating the efficacy of Mitomycin C in endoscopic DCR have been performed. An extensive search of literature revealed only few controlled studies over the past 15 years [4, 22-24] (Table 2). There are a few studies P.J. Wormald [14], Rebeiz [25] where powered instruments were used but their success rates were comparable to our result. Watts et al [26] had found that there was no significant difference in the success rate of EnDCR with local application of 5–Fluorouracil compared to published reports of EnDCR without anti-metabolites.

The natural wound healing process – namely haemostasis, inflammation, proliferation and re-modelling that take place in a sequential manner – has an important influence on the patency of the rhinostomy opening [1]. This normal process is reported to be responsible for EnDCR and ExtDCR failures by causing:

1. Primary ostium closure
2. Formation of synechiae with middle turbinate
3. Formation of synechiae with septum and
4. Formation of granuloma within the ostium [4].

Conclusion

EnDCR has a definite role on chronic dacrocystitis. Dacrocystitis is a disease commonly affecting the lower and middle socio-economic group and most commonly affecting females. EnDCR has many advantages over the standard external DCR. With a good success rate, EnDCR avoids an external scar, produces minimal postoperative discomfort, and maintains the pumping action of orbicularis oculi.

Simultaneous correction of nasal septal deviations and other nasal abnormalities is possible, thus reducing the chances of failure. EnDCR with Mitomycin C shows beneficial effect in preventing closure of the rhinostomy stoma and is preferred treatment of choice in case of chronic dacrocystitis with higher success rate and minimal postoperative complications. Meticulous, atraumatic surgical technique is of paramount in achieving a successful result.

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