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ORIGINAL ARTICLE

Study of Endonasal Endoscopic Dacryo-cystorhinostomy with Special Reference to Mitomycin-C

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Abstract The aim of this study was to evaluate long-term results in patients with nasolacrimal duct obstruction treated with intranasal endoscopic dacryo-cystorhinostomy (DCR) with intraoperative topical application of mitomycin-C. The procedure was carried out in 34 subjects (41eyes). Patients with post-saccal stenosis were divided into two groups, 21 patients were treated with intranasal endoscopic dacryo-cystorhinostomy with intraoperative application of Mitomycin-C (MMC) and the other 20 cases underwent procedure only without Mitomycin-C. Effectiveness of drug at rhinostomy site was assessed in relation to granulation formation, adhesions and ostium size. Outcomes were assessed on the basis of relief of subjective symptoms, patency of rhinostomy site confirmed via syringing and final ostium size at end of 6 months, 1 and 2 year. Success rate was 100% at 3 and 6 months follow-up in both the groups. At the end of 1 year, one failure was noted in control group which had to undergo revision endoscopic DCR with overall success rate decreasing to 97%. This was maintained at the end of second year. Results revealed that adjunctive use of Mitomycin-C was effective at 3 months when granulation tissue formation was significantly lesser in MMC group compared to no MMC group. Topical application of Mitomycin-C has been found to be beneficial in preventing adhesions and also resulted in larger neo-ostium. We concluded that results with intraoperative topical application of Mitomycin-C in endoscopic dacryo-cystorhinostomy are encouraging. It can favourably affect wound healing and result in larger rhinostomy size/ostium. Mitomycin-C is safe and effective adjunct in endoscopic dacryo-cystorhinostomy procedure.

Level of evidence Individual prospective cohort study, level 1b

Keywords Mitomycin-C · Endoscopic dacro-cystorhinostomy · Rhinostomy

Abbreviations

MMC	Mitomycin-C
ENDO-DCR	Endoscopic dacryo-cystorhinostomy

Introduction

Dacryo-cystorhinostomy (DCR) is a surgical procedure indicated in patients with nasolacrimal duct obstruction (post-saccal) performed to re-create normal lacrimal drainage into the nose. Mostly the cause of obstruction is idiopathic. Amongst the known etiopathological factors, dacryo-cystitis is the commonest. It becomes more common with increasing age, shows a female preponderance with epiphora as the commonest presentation.

In 1893 Caldwell was the first to propose endonasal approach of DCR [1]. However, due to limited technology at that time, the external approach was gold standard line of management. The advent of endoscopes with different degrees of angulation for endoscopic sinus surgery and advancement of optics in 1950s popularised the use of

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endoscopic DCR. The first clinical study was published by Mc-Donogh and Meiring in 1989 [2].

The advantages of endoscopic approach are excellent visualization, improved haemostasis, minor traumatisation, no external scar, preservation of lacrimal pump function, reduced hospital stay, reduction of surgical time, ability to treat the coexisting sinonasal pathology simultaneously in addition to correction of common causes of DCR failure. The success rate of endoscopic DCR is comparable to that of traditional external procedure [3, 4] and it should also be considered for revision surgery in patients who have a failed external DCR [5].

However, fibrosis, postoperative adhesions and scarring of the rhinostomy site leading to obstruction of the common canaliculus is one of the commonest reason for failure in endoscopic DCR [6].

Different modalities in ENDO-DCR surgery such as Stents and intraoperative antiproliferative adjuncts like Mitomycin- C (MMC) and 5-Flourouracil have been used to enhance the success rate [7].

In this study results with intraoperative use of MMC at the rhinostomy site has been evaluated. The reasons for failure of endoscopic DCR have also been assessed.

Materials and Methods

41 (eyes) cases with chronic dacryocystitis with acquired causes of nasolacrimal duct obstruction, idiopathic or secondary to infection or traumatic cause (with or without mucocele, with or without fistula) in normal or dilated lacrimal sac attending ENT and HNS OPD in a rural based hospital from 1st September 2007 to 1st September 2009 were included in the study.

Patients with common canalicular block, neoplastic causes leading to chronic dacryo-cystitis and previous dacryo-cystorhinostomies either by external or endoscopic approach were excluded from the study.

This is a prospective comparative study in which all cases underwent detailed history followed by general physical, ophthalmic and ENT examination. NLDO had been confirmed by syringing via the lacrimal puncta. Other causes of watering eye were excluded. Routine haematological investigations were done. Amongst the radiological investigations, only X ray PNS was done to assess the sinus condition. Dacryo-cystography and CT scan were reserved for special cases.

After consent, the operation was performed under LA. However, apprehensive patients were given the option of GA. Endo-DCR was performed in 41 eyes. The rhinostome created was approximately 10–12 mm. The opening of rhinostomy was measured in vertical dimension using a specially graduated probe marked at 1 mm intervals. The opening of common canaliculus was seen through the rhinostome using 30° endoscope. Syringing was done to confirm the patency after dilatation of the lower punctum. In every alternate case, a surgical sponge, soaked in 0.5 mg/ml solution (5 mg of MMC diluted with 10 ml of sterile water) of Mitomycin-C, was applied to the mucosal border of the rhinostomy site for 2.5 min. After removal of the sponge, the area was irrigated thoroughly with saline solution and aspirated. A change in the colour of the nasal mucosa from pink to white -grey was visible immediately after application.

The nasal endoscopy findings, details of procedure and complications were recorded in the prescribed proforma. A systemic oral antibiotic based on culture and sensitivity report (ciprofloxacin), analgesics, combination of antihistaminics and decongestants were started in the postoperative period. On 2nd day morning patient was discharged after syringing. Follow up was done on 3rd day, 7th day, 1, 3, 6 month, 1, $1^{1/2}$ and 2 year interval. In the postoperative visits clinical examination, syringing and nasal endoscopy was carried out to see and remove any crust, granulation and synaechiae at the rhinostomy site. Nasoendoscopic findings were recorded at the completion of the surgery and at 3, 6 month, 1 and 2 year. The parameters recorded were ostium size, granulation formation and adhesions/synaechiae formation. Patency by free flow during syringing and subjective relief of symptoms in postoperative period were noted to assess the success rate.

t—Test and Fisher's exact Test were used to calculate the statistical significance.

Results

The study was carried out in 34 subjects (41 eyes) in a rural based hospital, of which 29 were females and 5 were males. The age group ranged from 25 to 92 years. Out of 41 endoscopic DCR procedures, MMC was applied in 21 cases (51%) intraoperatively while 20 cases (49%) were taken as control in which no MMC was applied.

Complications encountered during endoscopic DCR were bleeding (minimal), granulations, synaechiae, pain over root of nose and swelling over lower eyelid.

Granulation formation (38, 93%) (Table 1) was noted in almost all cases with or without MMC and was maximum at 3 months postoperatively (critical period). At the 3 months postoperative period, granulation formation was seen in 18 cases (86%) in the case group and in 20 cases (100%) in the control group. However, it was minimal in MMC group compared to exuberant granulations in control group (Fig. 1).

Figure 1 showing granulations present at the rhinostomy site marked by arrow in the individuals who underwent

Table 1 Granulation at 3 months post operatively (n = 41)

MMC	Granulation		Total
	Present	Absent	
Applied	18 (86%)	3 (14%)	21
Not applied	20 (100%)	0 (0%)	20
Total	38 (93%)	3 (7%)	41 (100%)

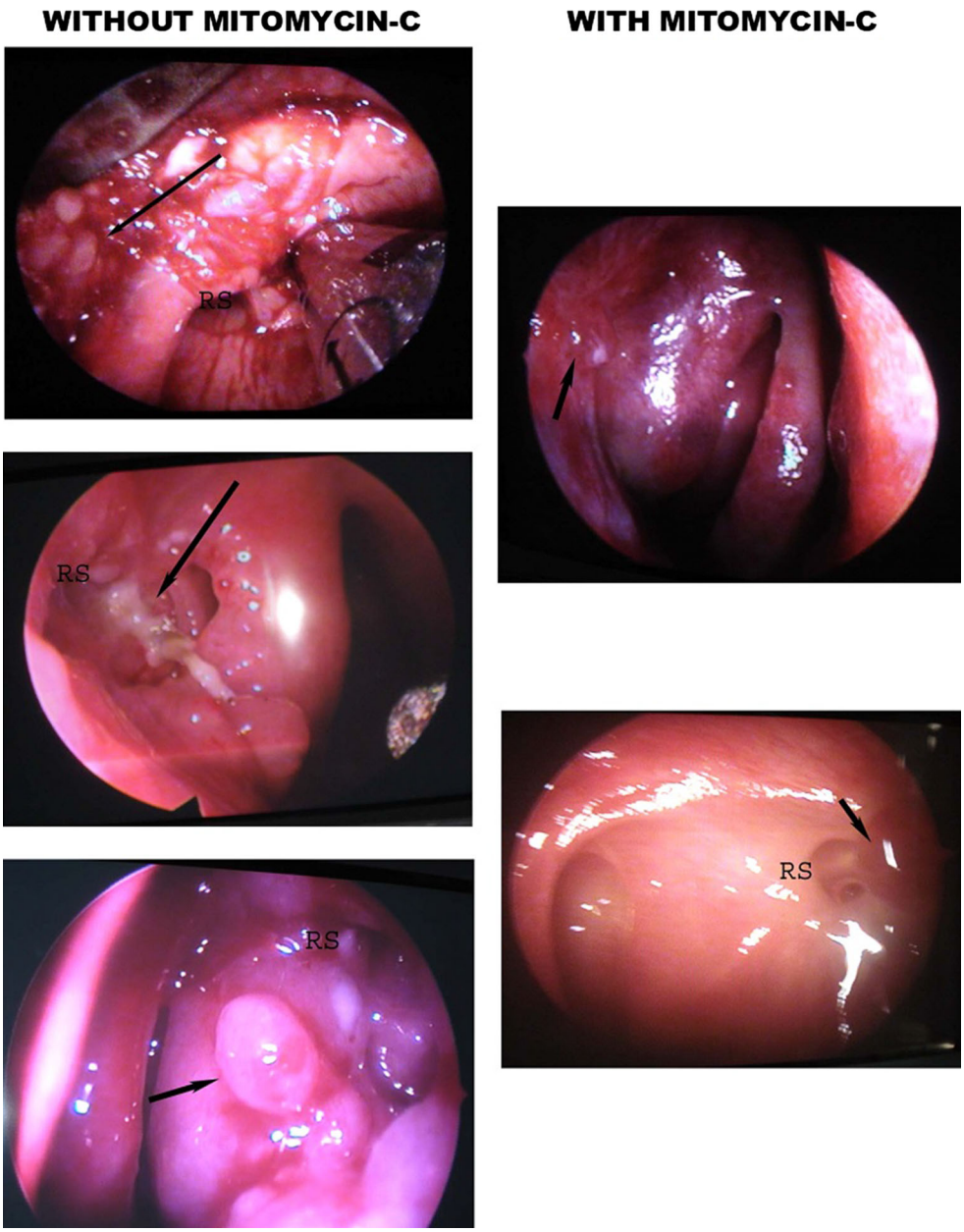

Fig. 1 Granulations present in post-operative cases of endoscopic dacryocystorhinostomy at 3 months. *RS* rhinostomy site

endoscopic dacryo-cystorhinostomy. The left column shows presence of granulation at the rhinostomy site where mitomycin-C has not been used whereas, the right column shows pictures of relatively granulation free rhinostomy site where mitomycin-C was used.

At the 6 months postoperative period (Table 2), granulation was seen only in 4 cases (19%) in the case group and in 20 cases (100%) in the control group. On application of Fisher's exact test, $p = 0.000000$. Since $p < 0.05$, highly significant disappearance was noticed.

In the MMC group (n = 21), at the six months postoperative period, the rhinostomy size of 10 patients (47.6%) was more than 10 mm in vertical dimension, another 10 patients (47.6%) had their rhinostomy size ranging from 7 to 9 mm and only one patient (4.76%) had its size between 4-6 mm size (Table 3). In the control group (n = 20), most patients (17, 85%) had their ostium size between 4 and 6 mm and 3 patients (15%) had their size in the range 1–3 mm. None had their size $\geq$ 7 mm (Fig. 2). On application of *t* test, calculated t was 2.02 signifying *p* value < 0.05 suggesting significant difference.

Figure 2 shows comparatively bigger and well epithelialized rhinostomy site in the mitomycin-C (right column) group than the non MMC group (left column) at 3, 5 and 6 months respectively. Rhinostomy site is marked by arrows.

Only 20 patients followed up for 1 year (Table 4), 12 cases were from MMC group while 8 were from No MMC group. 8 patients in MMC group (66%) had their ostium size between 7 and 9 mm while 3 patients (25%) had the size between 4 and 6 mm and only one (8.3%) fell in the range of 1–3 mm. None resulted with complete closure of the ostium. In the control group, most patients (n = 6, 75%) had their ostium size between 1 and 3 mm while one patient (12.5%) had the ostium size 4–6 mm. At the end of 1 year, one patient in the control group resulted in failure due to complete obstruction (Fig. 3). On application of t-test, calculated t was 2.10 signifying *p* value < 0.05 suggesting significant difference.

Figure 3 shows comparatively bigger and well epithelialized rhinostomy site in the mitomycin-C (right column) group than the non MMC group (left column) at 9, 12 and 24 months respectively. Rhinostomy site is marked by arrows.

Synaechiae formation was seen in (20, 49%) cases. The most common site of synaechiae formation following endoscopic dacryo-cystorhinostomy was between the middle turbinate and the lateral nasal wall in 14 cases (70%) followed by those formed between the septum and middle turbinate in 3 cases (15%) and between septum and inferior turbinate in 3 cases (15%). Amongst 41 procedures, synaechiae release with splint insertion was done in 9 cases (22%), granulation removal in 2 cases (5%), followed by widening of rhinostomy in one case (2%) and revision endoscopic DCR done in one case (2%).

At 6 months, there was relief of subjective symptoms in all the patients (100%). At the end of 1 year, failure resulted in one subject of control group (2.8%) while rest 34 patients (97%) reported complete relief from their subjective symptoms. The patients who did not turn up for follow up visits were assessed on telephonic conversation and by postal survey. At the end of 2 years out of 30 cases that could be assessed, relief of subjective symptoms was found in 29 cases (97%) with failure resulting in one case which belonged to No MMC (3%).

Success rate at the end of 3 months was 100%. This was maintained till 6 months with a fall to 97% at the end of 1 year. At the end of 2 years the success rate was maintained at 97%.

Discussion

The aim of this study was to evaluate the long-term results with mitomycin-C in intranasal endoscopic dacryo-cystorhinostomy with topical application of mitomycin-C. Mitomycin C, an antimetabolite well known for its antitumor activity, is isolated from *Streptomyces caepitosus*. It selectively inhibits the synthesis of DNA at low concentrations but can suppress cellular RNA and protein synthesis at higher concentrations and can lead to chromosomal aberrations. Topical application of Mitomycin-C, an antimetabolite with antifibroblastic action on fibroblasts, has been found to be beneficial in preventing adhesions and granulation formation [8, 9]. The most

Table 2 Granulation at 6 months postoperatively (n = 41)

MMC	Granulation		Total
	Present	Absent	
Applied	4 (19%)	17 (81%)	21
Not applied	20 (100%)	0 (0%)	20
Total	24 (59%)	17 (41%)	41 (100%)

Table 3 Rhinostomy size at 6 months postoperatively in mm (n = 41)

RS	No MMC	MMC	Total
Total obstruction	0	0	0
1–3	3 (7.2%)	0	39 (7.2%)
4–6	17 (41.8%)	1 (2%)	18 (44%)
7–9	0	10 (24.5%)	10 (24.5%)
≥ 10	0	10 (24.5%)	10 (24.5%)

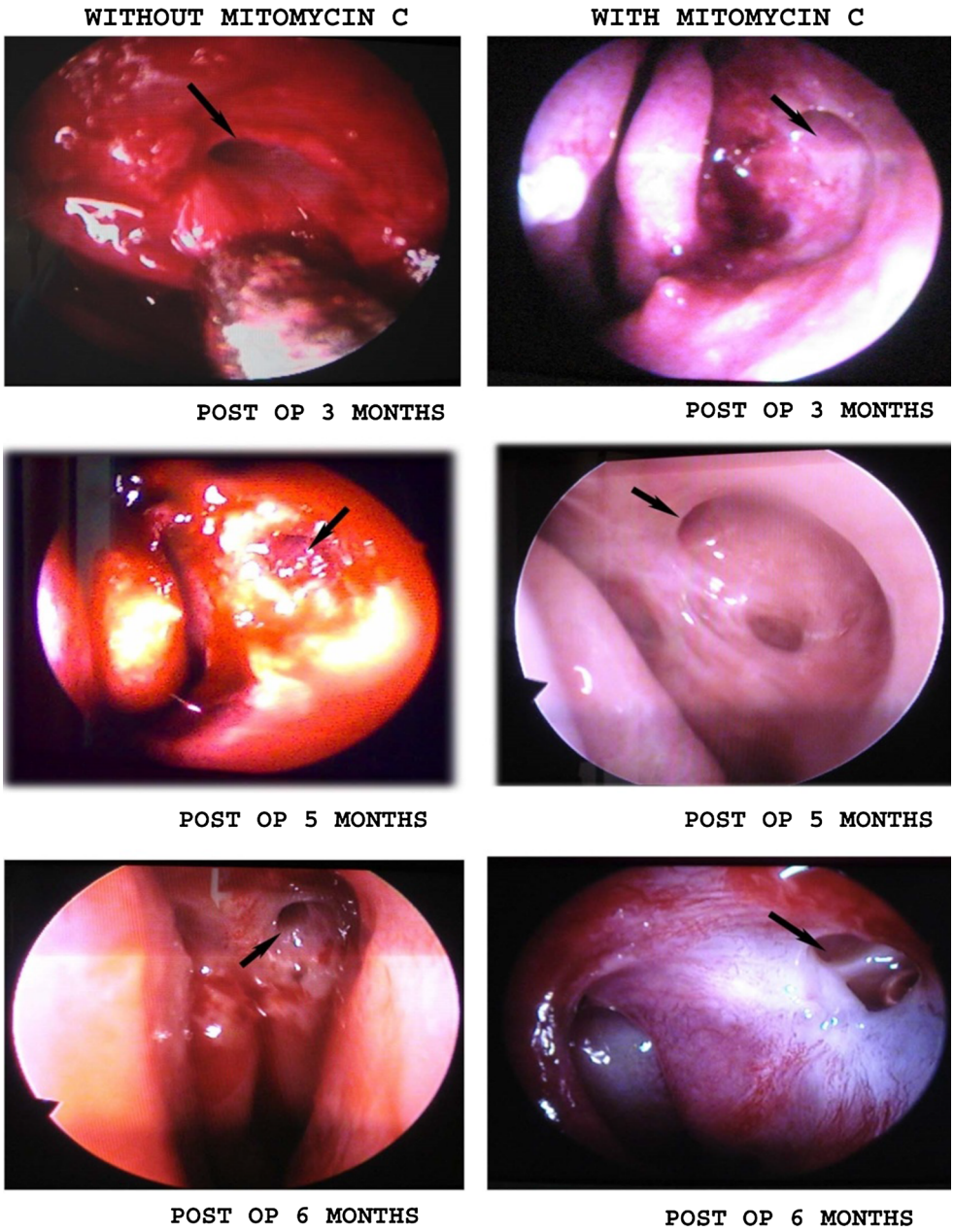

Fig. 2 Endoscopic view of size of rhinostomy in postoperative cases of endoscopic dacryocystorhinostomy

Table 4 Rhinostomy size at 1 year postoperatively in mm (n = 20)

RS	No MMC	MMC	Total
Total obstruction	1 (5%)	0	1 (5%)
1–3	6 (30%)	1 (5%)	7 (35%)
4–6	1 (5%)	3 (15%)	4 (20%)
7–9	0	8 (40%)	8 (40%)
≥ 10	0	0	0
Total no. of cases	8 (40%)	12 (60%)	20 (100%)

common complication encountered in our study was granulation formation seen in 38 (93%) patients postoperatively followed by synaechiae formation (20, 49%), the two being the main reasons for failure or closure of the rhinostomy window.

In our study granulation formation around the rhinostomy site was mostly seen around 2–3 months in both MMC and no MMC group. This is well supported in other studies by the fact that the fibroblastic activity of the tissues is high around the 3–4 months of procedure [10–13]. Studies indicated that the critical period was 3–6 months after endoscopic surgery and the onset of failure was high during this period. Rhinostomy closure by granulation tissue has been reported as the most important reason for failure in endoscopic lacrimal surgery [10, 13]. In our study, adjunctive use of mitomycin-C has favorably affected the outcome and success of the procedure. We found that though granulation tissue formation also occurred in the MMC group, but the adjunctive use of mitomycin-C has been found to be effective after a period of 3 months when the granulation tissue formation was significantly lesser compared to no MMC group. In our study, out of 38 (93%) cases in which granulation tissue was present (3 months postoperative period), 18 (44%) cases were in the MMC group and 20 (49%) cases in the control group. The value significantly reduced ($p < 0.05$) to 4 (10%) in the MMC group at 6 months post-operative period compared to control group where the value remained the same. However, no granulation was seen in the either group after a period of 6 months.

In our study, it was evident that at the end of 6 months postoperatively, all the patients in the MMC group (100%) had their ostium size ≥ 7 mm being considered in vertical dimension while all the patients in the control group had their ostium size ≤ 7 mm. The difference was statistically highly significant ($p < 0.05$). The results also revealed that ostium size contracted much faster in the control group as compared to that in the case group. At the end of 1 year, though half of the patients did not turn up for follow up visits, but the results revealed that the ostium size in the case group was comparatively much larger than the control group making the difference statistically significant. At the end of 2 years, the endoscopic examination of follow up patients again revealed the ostium size to be larger than that of the control group. The ostium size in MMC group ranged from 6 to 8 mm as compared to 2–3 mm in the control group. The decrease in size of the healed intranasal ostium after surgery is the result of a normal wound healing process. Antimetabolites like Mitomycin-C when used intraoperatively can favorably affect the wound healing process [14]. Our study finding is well supported by other authors [6, 15–18] with success rates approaching 87–99%.

Synaechiae formation was present in 20 (49%) cases. In our study, most common site for synaechiae formation was between the middle turbinate and the lateral nasal wall (14 cases, 70%) and it was mostly seen in the control group. This may be probably due to the raw area created between the middle turbinate and the lateral nasal wall. This represented a fallacy in our procedure where either there was inadequate or too much resection of the nasal mucosa. The removal of the nasal flap needs to be modified in our study. This can be possible by making horizontal cuts in the nasal flap superiorly and inferiorly based and thus covering the bare bone (Wormald technique) [19]. Inadequate or too much resection of the nasal mucosa can be one of the reasons for failure of endoscopic DCR [12]. Moreover, treating coexisting sinonasal pathologies at the same time may also result in synaechiae formation. This was done in two of our cases; one being that of high deviated nasal septum and other being minimal polyposis. The incidence of synaechiae formation was high in our study as compared with other few studies in which the reported incidence is less ranging between 4 and 9% [12, 20, 21].

Synaechiae removal was carried out in those cases which could cause significant nasal obstruction and those which were present between the middle turbinate and the rhinostomy site to avoid closure of the neo-ostium. In two cases, significant granulation was seen obscuring the rhinostomy site at the end of 3 months and patients returned with the complains of mild epiphora. Granulation removal was done in these cases and patients did well with it. In one of the patient the rhinostomy site was reduced to 2 mm size

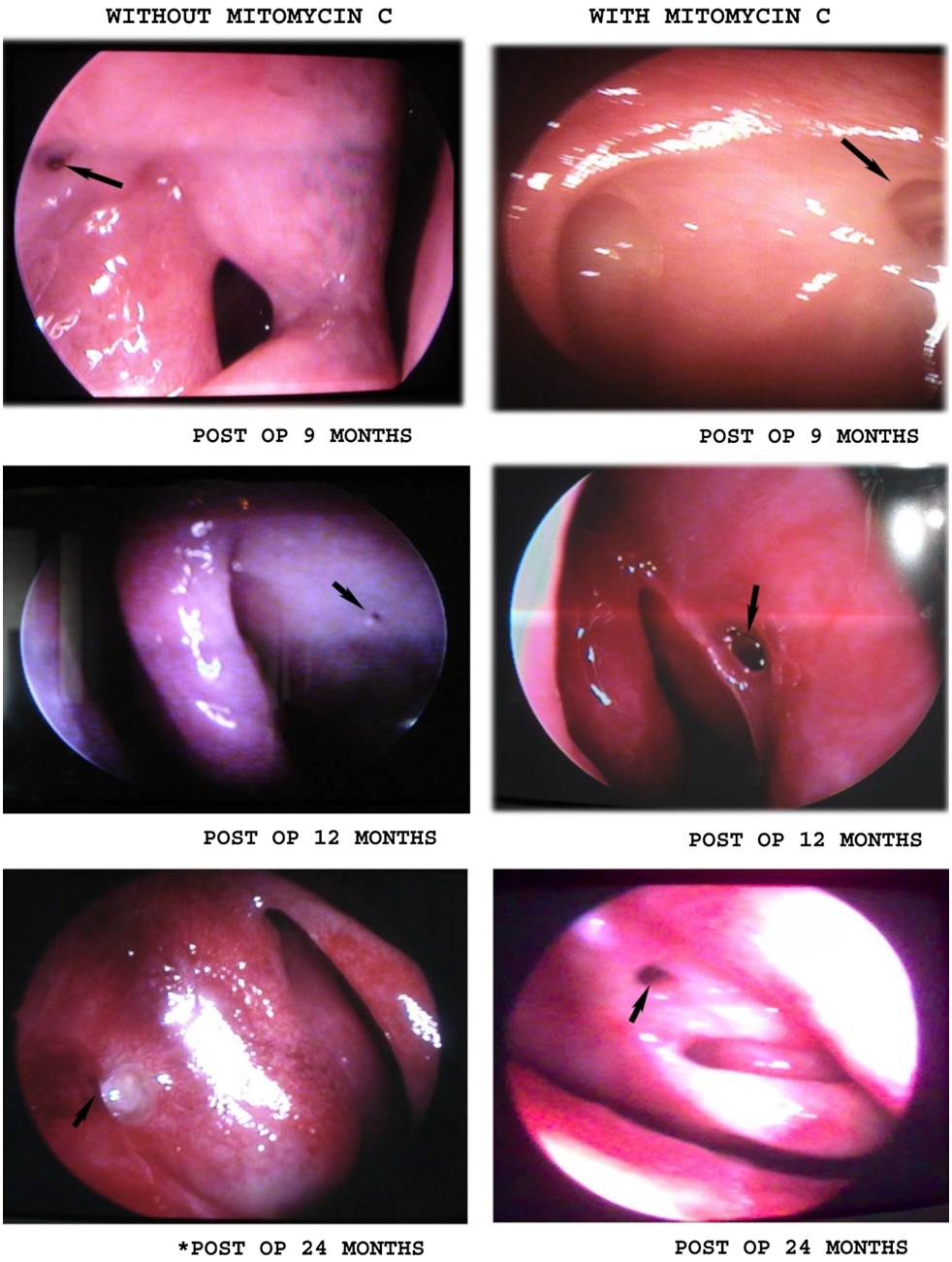

Fig. 3 Endoscopic view of size of rhinostomy in postoperative cases of endoscopic dacryocystorhinostomy. * Blob of mucus just visible on pressure over medical canthus

at the end of 6 months due to fast mucosal growth and widening of the rhinostome was carried out. Another patient returned with complains of epiphora at the end of 1 year and revision endoscopic DCR had to be carried out. The reason of failure was inadequate removal of the medial half of the sac and inadequate removal of the bony spicules which led to its ossification with the lateral wall causing obstruction. Leaving even one piece of the bone can result in ossification of the bony spicule with the lateral wall [12]. Moreover, this failure occurred in the control group where no MMC was applied. Significant granulation tissue formation and small size of the ostium might have in turn led to its closure.

When DCR fails, it appears to do so as a result of postoperative adhesions that obstruct the surgical ostium despite the presence of the stent [22]. Topical application

of Mitomycin-C has been found to be beneficial in preventing adhesions [8, 9]. Different concentration & time of application ranging from 0.2 to 1 mg/ml and from 2 to 30 min respectively have been used in various studies & their results are controversial. Although in some studies, MMC application resulted in a larger ostium and a better outcome compared with control patients who had no MMC [6, 15–18], others have found no significant difference between the two groups [21, 23]. In all studies, however, MMC had a high safety profile and no serious side effects were recorded. A study has shown that adjunctive use of MMC in higher concentrations as high as 1.0 mg/ml did not induce any permanent functional or histopathologic changes in the nasal mucosa in a rabbit model [24]. Another study showed that with higher doses of MMC (0.4 mg/ml for 2 min) the ostium still contracts significantly after 6 months of follow up, but the final size appears to be larger than the control group or the low dose MMC group (0.05 mg/ml for 2 min) [25]. In our study, majority of the cases belonged to low socioeconomic class so affordability was a major criterion. MMC costs INR135 per 2 mg vial. Multiple applications using a single vial are difficult, both because of the short shelf life of reconstituted MMC (2 weeks) and the relatively low incidence of cases requiring endoscopic DCR. Nevertheless, even with single application, we feel that using MMC as an adjunct to endoscopic DCR may still be more cost-effective than performing the revision procedures in its absence.

Success Rate

In our study, the outcome measures were assessed on the basis of relief of subjective symptoms and by patency of the rhinostomy site via syringing. The success rate was 100% in the 3 and 6 months follow up period. At the end of 1 year, one failure occurred which had to undergo revision endoscopic DCR. Thus, the success rate came down to 97% at the end of 1 year. This was seen in case without use of MMC. Out of the 30 cases at the end of 2 years, only one failure was reported and the success rate was maintained at 97%. The success rate of endoscopic DCR in our study is comparable with the other studies [8, 9, 14, 20, 21].

Conclusion

MMC is clinically efficacious in blocking adhesions and recurrence and its effect on the size of ostium is promising. The ability of this drug to modify the normal wound healing pathway by inhibiting fibroblast and endothelial cell growth and replication, has made it an attractive adjunct to DCR surgery. In our study, we concluded that topical application of Mitomycin-C intraoperatively is a safe and effective adjunct which results in a larger rhinostomy size/ostium and thus, enhances the success rate of endoscopic dacryo-cystorhinostomy.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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