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Original Research Study

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Role of Mitomycin C intraoperatively in improving the success rate of DCR surgery in paediatric population

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ABSTRACT

Aim: To establish the strength of association between intraoperative application of Mitomycin C (MMC) in pediatric Dacryocystorhinostomy (DCR) and its surgical outcomes., thereby determining the role of MMC in improving the success rate of DCR surgery in pediatric population.

Materials & Methods: It is a prospective observational study conducted at Gandhi Hospital Hyderabad & Sarojini Devi Regional Eye Institute Hyderabad. 60 Eyes of 60 children of different age groups ranging from one month to 15 years were included in the study. Our study population was the paediatric patients attending the out-patient department. They were recruited after informed consent was obtained from the patient's guardians and after getting confirmation from them for willingness for follow-up as per study guide lines. Those patients who were requiring DCR surgery were taken up for external Dacryocystorhinostomy in which 30 patients were randomly selected and subjected to cotton pledget soaked in topical MMC (0.002% or 0.2mg/ml) for 2 minutes. The study was conducted from Nov-2018 till Oct-2020.

Result: There was statically significant success rate of primary external DCR with the use of intra-operative MitomycinC over DCR without MitomycinC in congenital Nasolacrimal Duct Obstruction.

Keywords: Epiphora, Chronic Dacryocystitis, External Dacryocystorhinostomy, MitomycinC, Dacryocystogram & HCT(Helical Computed Tomography).

INTRODUCTION

Epiphora due to primary nasolacrimal duct obstruction is an often encountered in our society. The treatment of choice for congenital chronic nasolacrimal duct obstruction is external dacryocystorhinostomy (Ext-DCR) technique. The success rates achieved with this technique reached 94% in the 1920s (1).

Better endoscopic techniques focused on the major causes of failure of external surgery, like scarring within the anastomosis and the common canaliculus, closure of the

ostium by granulation tissue, adhesions to the medial wall of nose, and new bone formation. In pediatric age group narrow nasal cavities is an additional challenge.

Naturally, wound healing modulation with anti fibrotic agents like mitomycin c and 5 fluorouracil were the next logical adjuvanta to dcr. They aimed at preventing proliferation of fibroblasts' and thereby scar formation which could further potentially refine the success rate of dcr. Mitomycin c (mmc) is an alkylating agent which is used as an anti-cancer drug and it also is an antibiotic. It is derived from the streptomyces caespitosus. This has a property to

reduce collagen synthesis of fibroblasts by inhibiting dna dependent rna synthesis. It was being effectively used to improve outcomes of trabeculectomy surgeries since 1980.

As of now , only few trials have used intraoperative mitomycin c in ext-dcr and of them very few are done in pediatric age group. Further, most of them are not randomized controlled trails. The proposed study would thus contribute to the literature on use of mmc in ext-dcrs in pediatric age groups and the data thus obtained would formulate the protocols in indications, duration, and technique application of mmc.

Success rates of External DCR

Success varied between 65 and 100% after External DCR compared with Endonasal DCR, which varied from 84 to 94% (5)(22). The success rate of Laser assisted Endonasal DCR varied widely between 47 and 100%. The wide range of success rate may be related to patient demographics, surgical variability, and death of standardized outcome measures. Also the success rates are found to drop with passing time.

Factors noted to be the reason for failure are

- Fibrous tissue growth.
- Inappropriate size / location of bony ostium.
- Sump syndrome.
- Collapse of the bridge between anterior flaps.
- Adhesion of the anterior to the posterior flaps.
- Obstruction of the bony window with the new bone formation.
- Untreated common canalicular obstruction.
- Intranasal adhesions.
- Septate sacs incompletely connected to the nose.

Pediatric DCR

In pediatric group patients, management of Epiphora is a stepwise process starting with probing at the age of 9-12 months and the result in high cure rates.

For persistent watering and discharge following repeated probing, more invasive procedures like Balloon Dacryocystoplasty or external and endonasal Dacryocystorhinostomy are required in older children. DCR in the pediatric patients is not as predictable as in adults. In children, anatomy of the lachrymal passage is immature and rapidly changing along with a tendency towards vigorous scar tissue growth and closure of the osteotomy.

MITOMYCIN C (MMC)

This antibiotic was isolated from *Streptococcus caespitosus* by Wakaki and associates in 1958. It has limited clinical utility, having been replaced by less toxic and more effective drugs in most settings, except for anal cancers, for which it is curative. Mitomycin contains an azuridine group and a quinone.

Mechanism of Action

The drug inhibits DNA synthesis and cross links DNA at the N6 position of adenine and at the O6 and N7 positions of the guanine.

MMC in Ophthalmology

- A concentration of 0.2-0.4 mg/mL applied at subconjunctival or sclera locations intraoperatively during glaucoma filtration surgery and thus help in preventing scar formation in filtration bleb.
- It is also used after pterygium excision in same concentration to prevent recurrence.
- In DCR , it suppresses fibroblastic proliferation and scar formation under the flaps near osteotomy sites
- Topical MMC has been shown to reduce adhesions in postoperative period following a squint surgery.
- After a laser surface ablation in refractive surgeries, it prevents development of corneal haze
- MMC also aids in prevention of recurrence of localized conjunctival corneal intraepithelial neoplasia

It was concluded that short exposure to MMC causes cytotoxicity inhibits proliferation and also increases apoptosis of fibroblasts. Fibroblasts apoptosis decreases the number of cells available for proliferation and decreases product secretion for scarring.

Patients and methods

Study Design

This study is randomized, parallel group, placebo controlled interventional trial.

Study Population

Our study population was the pediatric patients attending the outpatient department of our hospital. The patients from Telangana and neighboring states were recruited after informed consent was obtained from patients guardians and after getting a confirmation from them on whether they were willing for a follow up as per the study guidelines since the study group included children of 7-15 yrs. 60 patients requiring DCR surgery were taken up for surgery in which 30 patients were randomly selected and subjected to cotton pledget soaked in topical MMC (0.002% or 0.2 mg/mL) for 2 mins.

Setting

The study was conducted from November 2018 till October 2020 in the department of Ophthalmology Sarojini Devi Eye Hospital, Hyderabad, India and Gandhi Hospital, Secunderabad, India.

Inclusion Criteria

Pediatric age group of 7-15 years with congenital chronic Dacryocystitis, failed cases of lachrymal intubation and probing in the same age group.

Exclusion Criteria

- Adults
- Acute Dacryocystitis
- Acute or chronic Dacryocystitis

- Secondary causes of Epiphora and Nasolacrimal duct obstruction like trauma and other causes
- Patients with recurrent abscesses and tumors
- Nasal pathologies like
- Symptomatic Deviated Nasal Septum
- Active Sinusitis
- Nasal Polyps
- Nasal Tumors
- Atrophic Rhinitis
- Revision DCR
- Patients not able to come for follow up
- Patients who do not consent for the enrollment into the study

Pre-Operative Evaluation

- History
 - Relevant history from the patient and guardians of patients main complaints
 - History suggestive of Dacryocystitis and its management
 - Birth History
 - Any ENT complaints
 - Any Co-morbidities like diabetes mellitus, Hypertension, Keloid tendencies, bleeding tendencies
 - Past Ocular / Lachrymal / ENT surgeries
- Best Corrected Visual Acuity
- Regurgitation on pressure over lachrymal sac (ROPLAS)
- Complete slit-lamp anterior and posterior segment examination
- Syringing of Nasolacrimal duct
- Radiographic tests like Dacryocystogram and Dacryoscintigraphy in few indicated cases

Technique of External Dacryocystorhinostomy

Pre-operative evaluation

- Nasolacrimal duct syringing
- Surgical profile which includes
 - Hemoglobin levels
 - Blood sugars
 - Blood pressure
 - Clotting time
 - Bleeding time
 - Viral markers

Pre-operative medications

- One day prior to surgery, patients were kept on nasal decongestant drops and systemic antibiotics
- All the cases for bleeding disorders by obtaining clotting time and bleeding time and obtained fitness from the anesthesiologists

Surgical procedure (15)

- General anesthesia was given by an anesthetist

- After cleaning and rapping , an incision of 1.5cm length was marked over the anterior lachrymal crest extending 4mm above and 10mm below in a curvilinear fashion, 3mm away from the medial can thus.
- The nasal mucosa was anesthetized and vasoconstrictor was applied by placing the nasal pack which is with above medications.
- Fifteen minutes before start of surgery, Ethmsylate intramuscular injection was given which will help in controlling intra operative bleeding
- Once the skin incision has been created, the Orbicularis muscle fibers were separated with blunt dissector and periosteum was exposed overlaying the anterior lachrymal crest and above and below.
- Mullers self retaining Haemostatic Retractor and Catpaw Retractors were used to expose the lachrymal sac and the floor
- Lachrymal sac was retracted laterally with the help of sac retractor and periosteum is dissected off the floor of the lachrymal sac and as well as lachrymal bone.
- Meanwhile strict homeostasis was maintained to visualize the structures.
- The Osteotomy was created in the floor of the lachrymal sac mainly in the thin lamina payracea and the bone punch was used for this purpose.
- Once the osteotomy is created it is enlarged to the size of nearly 9-10mm in diameter.
- During the entire procedure to maintain visualization of the structures, suction cannula was used to prevent pooling of the blood in the event of bleeding
- More frequently cotton gauze packing were used to control capillary bleeding
- Osteotomy was made between anterior and posterior lachrymal crests and nasal mucosa is identified. Then A cottonoid dipped in 0.02%
- MMC was placed at the site of osteotomy for 2 minutes and then it was irrigated with normal saline thoroughly in 30 patients (MMC Group)
- The Nasal mucosa was opened by a H shaped incision and both anterior and posterior flaps are created
- Next to negotiate the lachrymal sac, a vertical incision was made along the entire length of fundus and body, any contents were evacuated.
- Partial excision of both posterior flaps of the lachrymal sac and nasal mucosa was done
- Both the anterior flaps of the lachrymal mucosa and nasal flaps were sutured by using interrupted 6'0 vicryl sutures after completing the flap suturing, orbicularis muscles fibers closed with 6'0 vicryl sutures and the skin flaps.
- Immediate post OP day along with wound dressing lachrymal syringing was done, post OP follows up was according to the prescribed follow up schedule.
- In the post OP day topical antibiotic drops were prescribed for a period of 1 month and systemic antibiotics given for one week.
- Nasal decongestant drops for instillation and systemic anti-inflammatory drugs prescribed for five days
- Patient's attendants were clearly explained not to blow the nose with an instruction of emergency visit

to the hospital in case of bleeding from the nose on the operated side.

- All the cases have completed a minimum follow up of 6 months form the day of surgery



Preparation of MMC Solution

- One vial of commercially available Mitomycin C contains 2 mg of lyophilized powder
- For intraoperative topical application, we require a concentration of 0.02%
- To obtain, 10ml distilled water must be added in the vial, and 1 must be taken out
- Now this should be mixed in 9 ml of distilled water
- Thus a concentration of 0.02% MMC would be obtained which was then soaked in a cottonoid and used in the surgery.

Definition of Success

- Subjective success was defined as substantial improvement to no watering or occasional watering requiring dabbing less than twice a day

- Objective success was taken as syringing test to be positive which anatomical patency
- There should be fully or partially free flow on syringing of the ducts
- Overall success was defined as fully or partially patent lachrymal system with subjective improvement in tearing and objective improvement in tear drainage

Follow up

Patient was followed up at:

- One day
- One week
- One month
- 6 months

Sutures were removed at the 1st visit that is after one week.

Analysis 1

Age: The age of patients included in the study ranged from 7 years to 15 Table 1: Age Group distribution among study groups.

Age Group (years)	MMC n (%)	Control n (%)
7	6 (10)	4 (6.6)
8-10	14(23.3)	14(23.3)
11-14	9(15)	10(16.6)
15	1(1.6)	2(3.3)

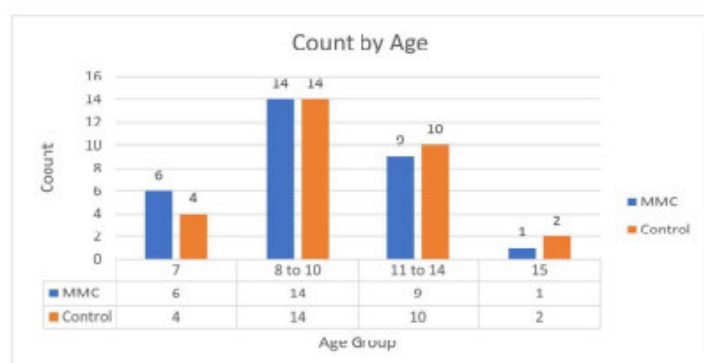


Chart 1: Age group distribution among study groups

Majority of patients were in the age group 8 -10

Results

Table 9: Overall Success Rate after 6 Months

MMC group n=30 (%)	Control group n=30 (%)	P value
29/30 (96.7)	28/30 (93.3)	0.546 (95% CI)

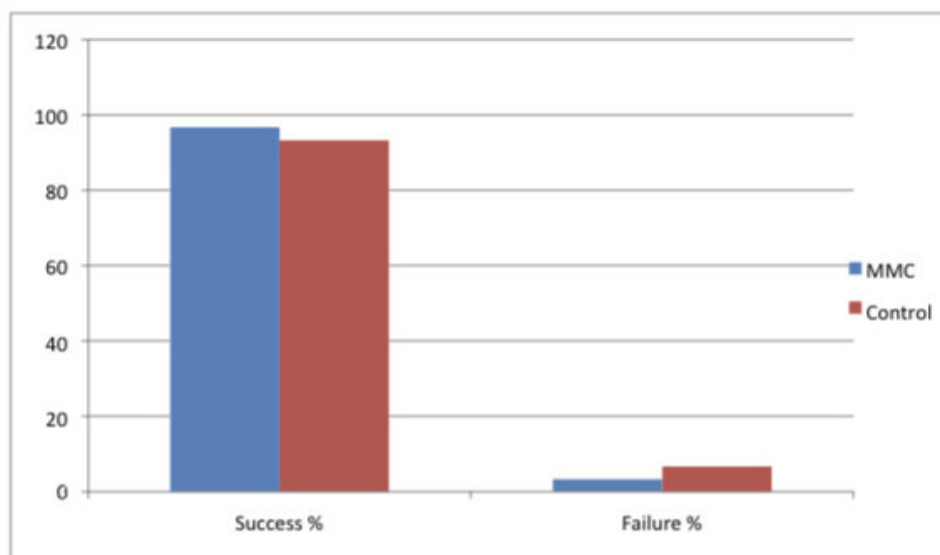


Chart 9: Overall success rate after 6 months

DISCUSSION

The prospective observational study was conducted at Sarojini Devi Eye Hospital, Hyderabad. 60 eyes of 60 children of different age groups ranging from 1 month to 15 years. were included in the study. All the patients had a follow up for minimum of 16 months.

Congenital Nasolacrimal duct obstruction is one of the most common causes of epiphora in children and external Dacryocystorhinostomy remains to be the gold standard surgical procedure even today. Major reasons reported for failure in DCR are scarring within the anastomosis and at the common canaliculus, closure of the ostium by granulation tissue, adhesions to the medial wall of nose, and new bone formation.

Thus the idea of antifibrotic agents came up, to prevent excessive fibroblast proliferation and scarring and thus improve the outcome of surgery. Mitomycin C was first used in 1980s to improve success in trabeculectomy surgeries and now it has established itself as a safe adjuvant in many other surgeries in ophthalmology (16) (17) (18). It is an alkylating agent used in cancer treatment and it inhibits DNA-dependent RNA synthesis thus reducing fibroblasts collagen synthesis.

The primary aim of our study was to find out the efficacy of MMC when used intraoperatively in congenital pediatric Nasolacrimal duct obstructions.

We studied 60 cases, which were randomized to a MMC group and a Control group of 30 each.

In the present study, most of the patients were found to be in the age group of 8-10 years. The next highest affected age group was 11-14 years. This distribution was seen in other studies as well.

Our study showed a slight male preponderance 32/60 (53.3%) patients being males. Previous studies suggested a female preponderance. However the male preponderance was not high and the difference in number of males and females was not very significant.

The overall success rate was 96.7% in the MMC group and 93.3% in the Control group and the difference was not statistically significant (p=0.546). This result was comparable with previous studies which used MMC in Ext-DCR. They had reported success rates between 90-100% for the MMC group and between 73-92% for the control groups. Only 4 studies could prove a statistically significant difference while the majority of studies showed no statistically significant advantage in using MMC.

Rose has described a “Lachrymal paradox” where anatomical success may not correlate to success in control of symptoms and vice versa. There could be a hydraulic resistance to the flow of tears from the lateral canthus to the nasal cavity even with a patent passage. Previous studies have also shown similar results. (19) (20)

The dose and duration of exposure of Mitomycin C is not standardized for the use of DCR. Previous studies doses ranged from 0.05-1 mg/ml with exposure time varying from 2 minutes to 30 minutes. Higher concentrations have shown to give better results as regards to final success and ostium size but the differences were not statistically significant. We used 0.02% for 2 minutes with good success outcomes. We did anterior lachrymal mucosal flaps suturing with nasal mucosa in this study. There were serious adverse effects of Mitomycin C noted in our study as has been with previous studies.

CONCLUSION

There was statistically significant success rate of Primary External DCR with the use of intraoperative Mitomycin C over DCR without Mitomycin C in congenital Nasolacrimal Duct Obstruction.

There were no complications related to the intraoperative use of 0.02% Mitomycin C for 2 mins in Primary External DCR.

However, more randomized control trials involving more participants and longer follow up are required to establish the potential benefits of antimetabolites in Primary DCR surgery.

REFERENCES

1. GI.H. Girgis Dacryocystorhinostomy J. Laryngol. Otol., 82 (2) (1968), pp. 149-152.
2. Harish V , Benger RS. The origins of lacrimal surgery, and evolution of dacryocystorhinostomy to the present. Clin Experiment Ophthalmol. 2013;n/a-n/a.
3. nChandler PA. Dacryocystorhinostomy. Trans Am Ophthalmol Soc. 1936;34:240-63.
4. 17. Yakopson VS, Flanagan JC, Ahn D, Luo BP. Dacryocystorhinostomy: History, evolution and future directions.Saudi J Ophthalmol. 2011 Jan;25(1):37-49.
5. Leong SC, Macewen CJ, white PS. A systematic review of outcomes after Dacryocystorhinostomy in adults. Am J Rhinol Allergy. 2010 Feb;24(1):81-90.
6. Quadir M, Ahangar A,Dar MA, Hamid S, Keng MQ. Comparative study of Dacryocystorhinostomy with and without intraoperative application of mitomycin C. Saudi J Ophthalmol [Internet], [Cited b2013 Nov 30]; Available from: <http://www.sciencedirect.com/science/article/pii/S1319453413001045>
7. Deka A, Bhattacharjee k, Bhuyan SK, Barua CK, Bhattacharjee H, Khaund G. Effect of mitomycin C on ostium in Dacryocystorhinostomy. Clin Experiment Ophthalmol.
8. Kao SC, Liao CL. Tseng JH, Chen MS, Hou PK, Dacryocystorhinostomy with intraoperative mitomycin C. Ophthalmology. 1997 Jan;(1):86-91.
9. You YA, Fang CT. Intraoperative mitomycin C in dacryocystorhinostomy. Ophthal plastReconstr Surg. 2001 Mar;17(2):115-9.
10. Liao SL, Kao SC, Tseng JH, Chen MS, Hou PK. Results of intraoperative mitomycin C application in dacryocystorhinostomy. Br J Ophthalmol, 2000 Aug;84(8):903-6.
11. Ari s, Gun R, Surmeli S, Atay AE, Caca I. Use of adjunctive mitomycin C in external dacryocystorhinostomysurgery compared with surgery alone in patients with nasolacrimal duct obstruction: A prospective, double-masked, randomized, controlled trail. Curr ther Res. 2009 Aug;70(4): 267-73.
12. yildirim C, Yaylali V, Esme A, Ozen s. Long-term results of adjunctive use of mitomycin C in external dacryocystorhinostomy. Int Ophthalmol. 2007 Feb;27(1):31-5.
13. Rahman A, Channa S, Niazi JH, Memon MS. Dacryocystorhinostomy without intubation with intraoperative mitomycin-C. J Coll Physicians Surg—pak JCPSP. 2006 Jul;(7):476-8.
14. Feng Y, Yu J, Shi J, Huang J, Sun Y, Zhao Y. A meta-analysis of primary external dacryocystorhinostomy with and without mitomycin C. Ophthalmic Epidemiol. 2012 Dec;19(6):364-70.
15. Yenugandula R, Prameela, kumar A. External dacryocystorhinostomyin paediatric patients and surgical outcomes- our experience in governement teaching hospital. J. Evolution Med. Dent. Sci.2018;7(45):0000-0000, DOI 10.14260/jemds/2018/0000.
16. Chen CW, Huang HT, Bair JS, Lee CC. Trabeculectomy with simultaneous topic application of mitomycin-C in refractory glaucoma. J Ocul pharmacol. 1990;6(3):175-82.
17. Abraham LM. Selva D, Casson R, Leibovitch I. Mitomycin: Clinical applications in Ophthalmic practice. Drugs. 2006;66(3):321-40.
18. Wilkins M, Indar A, wormald R. Intraoperative Mitomycin C for glaucoma surgery. Cochrane Database of systematic Reviews [Internet]. John Wiley & Sons, Ltd; 1996 [cited 2012 Aug 23]. Available from the below URL: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002897.pub2/abstract>
19. fayers T, Laverde T, Tay E Olver JM Lacrimal surgery success after external dacryocystorhinostomy: functional and anatomical results using strict outcome criteria. Ophthal Plast Reconstr Surg. 2009 Dec;25(6):472-5.
20. Rose GE. The lacrimal paradox: toward a greater understanding of success in lacrimal surgery. Ophthal Plast Reconstr Surg. 2004 Jul;20(4)262-5.
21. Pico G. A modified technique of external dacryocystorhinostomy. Am J Ophthalmol. 1971 Oct;72(4):679-90.
22. Mansour K, Sere M, Oey AG, Bruin KJ, Blanksma LJ. Long-Term Patient satisfaction of external Dacryocystorhinostomy. Ophthalmologica. 2005;219(2):97-100.
23. Satish1 K, Prakash2 DN. Tanwar3 M, Patil4 S, Gopal5 M, Acharta6 AA, et al. External DCR, Mitomycin C. Comp STUDY Extern DACRYOCYSTORHINOSOTOMY USE MITOMYCIN C [Internet].2013 Oct 23 [cited 2013 Dec 9];(2309). Available from the below URL:http://www.jemds.com/latest-articles.php?at_id=2309
24. Roozitaladb MH, Amirahmadi M, Namazi MR. Results of the application of intraoperative mitomycin C in dacryocystorhinostomy. Eur J Ophthalmol. 2004 Dec;14(6):461-3.
25. Gonzalvo Ibanez FJ, Fernandez I, Fernandez Tirado FJ, Hernandez Delgado G Rabinal Arbues F, Honrubia Lopez FM. [External dacryocystorhinostomy with mitomycin C. Clinical and anatomical evaluation with helical computed tomography] arch Soc Esp Oftalmol. 2000 Sep;75(9):611-7.