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To study efficacy and safety of probing with Mitomycin-c in adults with primary acquired nasolacrimal duct obstruction

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Abstract
Purpose: The study was conducted to study the effect of low dose of Mitomycin-C (0.2 mg/ml) as an adjunct for nasolacrimal duct probing to treat adults with primary acquired nasolacrimal duct obstruction and to study the side effects of MMC during probing.
Material and methods: It was a prospective, comparative, randomised interventional study. Patients were randomly divided into two groups of 20 each. Cases (20 eyes) with primary acquired NLD obstruction were treated with probing and intraoperative Mitomycin-C and controls (20 eyes) with primary acquired NLD obstruction were treated with only probing. At the end of 4 months, subjective improvement in epiphora and patency on syringing were evaluated.
Results: On follow up at 4 months, 35% cases showed mild improvement compared to 25% of controls. Moderate improvement was seen in 10% of cases compared to 5% of controls. Complete improvement was seen in 15% of cases compared to 0% of controls. The overall subjective improvement was seen in 60% of cases compared to 30% of controls. On syringing, NLD was found patent in 15% of cases compared to 5% among controls at 4 months follow up.
Conclusion: Our study confirmed the efficacy of probing with MMC in reducing the symptoms of epiphora with fewer side effects in patients with NLDO during 4 months of follow-up.

Keywords: Nasolacrimal duct obstruction, Mitomycin C, epiphora

1. Introduction
Primary acquired nasolacrimal duct obstruction (NLDO) is a syndrome of unknown origin and is the major contributing factor for epiphora in adults, with the exception of hypersecretion. It has been postulated that inflammation of unknown cause may result in fibrosis [1] of the nasolacrimal duct. Dacryocystorhinostomy (DCR) and canaliculodacryocysto-rhinostomy are the recommended surgical managements. In addition, it has been demonstrated that passing a probe down the nasolacrimal duct is an easy and safe alternative method [2, 3]. However, the risk of induced trauma and recurrent obstruction from further fibrosis after the procedure of probing is a major problem.
To prevent fibrosis due to probing and in order to improve subjective as well as objective outcome, MMC can be used as an adjuvant for nasolacrimal probing. MMC is a chemotherapeutic antibiotic that has been used as an adjunct to prevent recurrence after pterygium surgery and glaucoma surgery [4]. It inhibits fibroblast proliferation and prevents obstruction from fibrosis after probing. The purpose of our study was to study the safety and efficacy of the adjunctive use of low-dose MMC (0.2 mg/ml) for lacrimal probing to treat adults with blocked nasolacrimal ducts and to study the side effects of MMC during probing.

2. Material and Methods
This was a prospective, comparative, randomised interventional study that was conducted in 40 patients with primary acquired NLDO who attended Oculoplasty Clinic in Regional Institute of Ophthalmology, Pt. B.D. Sharma PGIMS, Rohtak, Haryana. Patients were randomly divided into two groups of 20 each. An informed consent was taken from all the patients.
The patients of >18 years of age of either sex having history of primary epiphora of less than 1 year duration and those in whom syringing showed regurgitation of fluid with or without pus from opposite punctum and were diagnosed with NLD obstruction were included. Patients with congenital NLDO, watering with patent passage, in whom syringing showed regurgitation from same punctum, previous trauma, recurrent dacryocystitis, any lacrimal

apparatus surgery and any other obvious cause for block, those with nasal structural abnormalities or nasal cavity pathologies, any other factor leading to hyperlacrimation were excluded from the study. Pregnant women were also excluded from the study.

A detailed history regarding age, sex, mode of disease onset and duration of the watering of the eyes was taken. Amount of tearing was categorized according to Kraft and Crawford [5] description given in 1982as:

- (-) no watering.
- (1 +) if epiphora outdoors.
- (2 +) if epiphora indoors with some source of irritation.
- (3 +) if constant epiphora.

Visual acuity was recorded using Snellen's chart. Anterior segment examination on slit lamp was done to rule out disorders of the ocular surface and eyelid examination was done for possible laxity or misdirected lashes and proper closure. When needed, tear break up time, Schirmer 1 and 2 test and Jones dye test 1 was performed. This examination and tests helped us to exclude cases of hypersecretion. Regurgitation test was performed by steady pressure with the thumb applied over lacrimal sac area below the medial palpebral ligament.

Lacrimal irrigation with saline solution was performed to know location of obstruction. Once complete NLD block was confirmed with the help of syringing and diagnostic probing, the patients were assigned to either group.

Group 1: Study group of 20 patients - probing with Mitomycin-C was done.

Group 2: Control group of 20 patients - only probing was done.

2.1 Procedure of probing

A single surgeon performed all the procedures. Nasal examination was done in all patients. Probing was done under local anesthesia using 0.5 percent proparacaine for topical anesthesia and 2 percent xylocaine with adrenaline for local infiltration around the medial canthus, the lower lid and deep upto the periosteum. The upper puncta was dilated using punctum dilator. A snuggly fitting Bowman's probe (0 and 00 probe) was passed in duct through the upper punctum. The probe was pushed through by use of gentle pressure and was advanced to the point of obstruction. Patency after probing was confirmed by syringing.

In the study cases, this was followed by irrigation with 1 mL of Mitomycin-C (0.2mg/mL, once) into the duct with a nasal pack in place for 10 minutes to minimize systemic absorption of MMC. The patient was instructed not to swallow the solution, followed by gargling with water to clear any residual MMC. Irrigation of the ocular surface was done immediately with 10 mL of physiological saline.

A single evaluator performed post procedure evaluation. The patients were followed up at 2 weeks, 1 month, 3 months and 4 months. At each follow-up, the patients were questioned about watering for subjective evaluation of improvement, and syringing was done at each visit to confirm the duct patency. Special attention was paid to the length of time free of symptoms (symptom free period). Slit-lamp examination of the caruncle, punctum, cornea, conjunctiva, iris, lens and anterior chamber along with nasal mucosa examination was done to look for any side effects.

Criteria for improvement was taken as

- Complete improvement was defined as no watering.
- Moderate improvement was defined as shifting of patient from 3 + to 1 +.
- Mild improvement was defined as shifting of patient from 3 + to 2 + or 2 + to 1 +.

3. Results

The age of cases ranged from 23-58 years with a mean of 46.55±9.271 years and in the controls ranged from 21-56 years with a mean of 40.95±10.465 years.

Table 1: Distribution of cases and controls by age

		Group		Total n (%)
		Cases n (%)	Controls n (%)	
Age group in years	20-29	1(5%)	2(10%)	3(7.5%)
	30-39	4(20%)	6(30%)	10(25%)
	40-49	6(30%)	7(35%)	13(32.5%)
	50-59	9(45%)	5(25%)	14(35%)
Total		20(100%)	20(100%)	40(100%)
Mean of age group		46.55±9.271	40.95±10.465	43.75±10.16
p value		0.582		

Among cases, 11 (55%) were females and 9 (45%) were males and coincidentally, in controls also there were 11 (55%) females and 9 (45%) males. In cases, out of 20 eyes, obstruction was seen on right side in 12 patients (60%) and on the left side in 8 patients (40%). In controls, out of total 20 eyes, obstruction was seen on right side in 8 patients (40%) and on left side in 12 patients (60%).

Table 2: Distribution of cases and controls by laterality

			Group		Total (%)
			Cases (%)	Controls (%)	
Laterality	Right	Count	12(60%)	8(40%)	20 (100%)
	Left	Count	8(40%)	12 (60%)	20 (100%)
p value			0.221		

During pre op evaluation, there were no patient with grade (-) or no watering in both the groups. In our study, patients having mild watering or grade 1+ of watering were 1(5%) among cases and 0 (0%) among controls. The maximum patients i.e. 10 (50%) patients among cases and 11 (55%) among controls had complaint of moderate watering or grade 2+ of watering. Patients with severe watering or grade 3+ were 9 (45%) patients among cases and 9 (45%) patients among controls.

Table 3 shows the comparison of complete, moderate, and mild subjective improvement at each follow-up with their p values. At 4 months, 35% cases showed mild improvement compared to 25% of controls. Moderate improvement was seen in 10% of cases compared to 5% of controls. Complete improvement was seen in 15% of cases compared to 0% of controls. Overall improvement was seen in 60% of cases compared to 30% of controls.

Overall improvement difference between two groups was found to be statistically significant at 4 months (p value <0.001). It was observed that the comparison of complete improvement was statistically significant at follow up of 2 weeks, 3 months and 4 months and statistically insignificant at 1 month. Howeever, the overall improvement difference in two groups was found to be statistically significant at all follow up periods.

Table 3: Distribution of cases and controls by improvement at various follow up

Follow up	Mild improvement (%) A			Moderate improvement (%) B			Complete improvement (%) C			Overall improvement (%) (a+b+c)		
Subjects	Cases	Controls	p value	Cases	Controls	p value	Cases	Controls	P value	Cases	Controls	p value
2 weeks	15	35	0.001	25	15	0.077	40	15	<0.001	80	65	0.018
1 month	20	25	0.397	20	10	0.048	30	5	0.384	70	40	<0.001
3 months	25	35	0.123	15	10	0.285	25	0	<0.001	65	45	<0.004
4 months	35	25	0.123	10	5	0.179	15	0	<0.001	60	30	<0.001

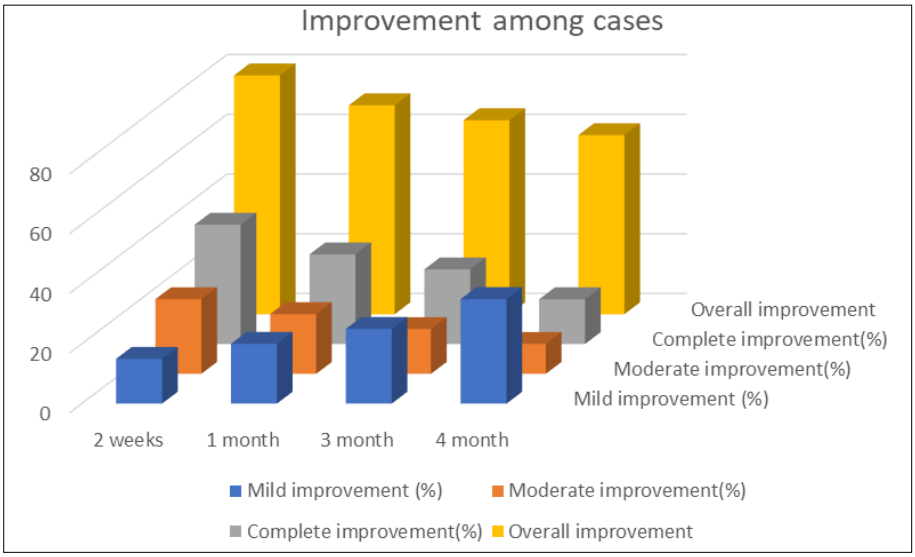

Fig 1: Distribution of mild, moderate, complete and overall improvement at various follow ups among cases.

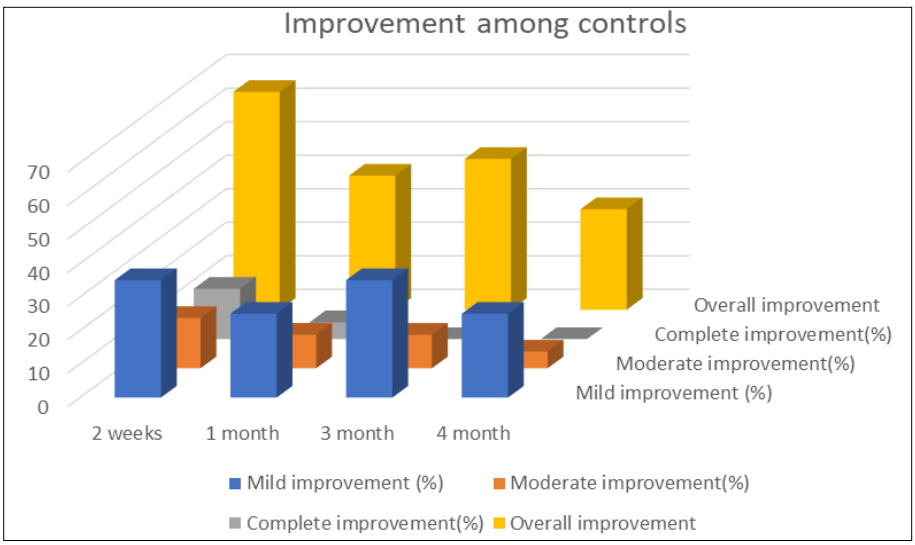

Fig 2: Distribution of mild, moderate, complete and overall improvement at various follow ups among controls.

All patients included in the study had pre op syringing results of regurgitation of fluid from opposite punctum. Probing was done in all cases and on post-operative evaluation of the patency of the lacrimal system by syringing at 2 weeks,1 month, 3 months and 4 months as shown in Table 4, we found patency in 15 (75%) patients, 11 (55%) patients, 5 (25%) and 1 (5%) patient among cases and 8 (40%) patients, 3 (15%) patients, 3(15%) patients and 1 (5%) patient among controls respectively with p value of <0.001,<0.001,0.077 and 0.081 at 2 weeks, 1 month, 3 months, 4 months respectively.

The results of patent NLD at follow up weeks were found to be statistically significant at 2 weeks and 1 month. The results were insignificant at 3 months and 4 months of follow up.

Table 4: Total no of patients in each group with patent nasolacrimal duct

Follow up	Cases % (n)	Controls % (n)	p value
2 weeks	75 (15)	40 (8)	<0.001
1 month	55 (11)	15 (3)	<0.001
3 month	25 (5)	15 (3)	0.077
4 month	15(3)	5 (1)	0.081

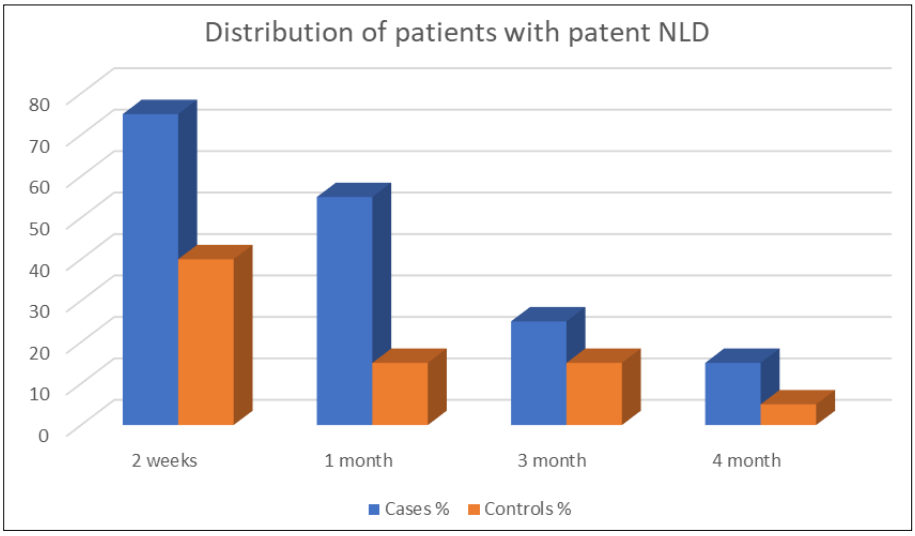

Fig 3: Distribution of cases and controls with patent nasolacrimal duct at various follow ups

Side effects of MMC were also kept in mind and observed among cases in anterior segment of the eye as well as nasal mucosa. However, no side effects of MMC were observed in any of the cases.

4. Discussion

Probing in adults is quick, safe, easily performed under local anaesthesia, cost effective and potentially an outpatient procedure. Compared with DCR, probing not only avoids cutaneous scarring but also preserves the functional pump mechanism of tearing by maintaining the integrity of the orbicularis muscle and medial palpebral ligaments. Probing provides an alternative treatment of choice for elderly patients who are poor surgical candidates or for those who do not wish to undergo DCR [4].

However, the risk of induced trauma and recurrent obstruction from further fibrosis is a major problem with probing. To prevent fibrosis due to probing, MMC is a new innovation. MMC inhibits DNA synthesis in all phases of the cell cycle because of cross-linkage between the DNA base pairs adenine and guanine. MMC also induces breakage of single-stranded DNA [6, 7]. Moreover, MMC prevents fibroblast proliferation and modifies the wound healing response, leading to less scarring and fibrosis around the common osteotomy and canaliculus site [8, 9].

Of the 40 patients who were enrolled for the study, none were lost to follow up. There was no statistical significance observed with regard to age, gender, duration of symptoms and laterality. There were significant differences between two study groups in patient's post probing epiphora grades during 2 weeks, 1 month and 3 months of follow up (p value 0.046, 0.050 and 0.020 respectively). Receding trends in grades of watering were seen i.e. the severity of watering increased with time and more patients shifted from grade 1+ to grade 3+.

In our study, on evaluating the patency of the lacrimal system by syringing, the difference in two groups was significant at 2 weeks and 1 month. (p value less than 0.001 at 2 weeks and 1 months). By the end of study, difference in patency of NLD became insignificant at follow up of 3 months and 4 months (p value 0.077 and 0.081 respectively) indicating closure of NLD.

The patency of the lacrimal system decreased with time in both groups. However, the results at all follow ups were better in cases than controls. In addition, this study indicated no significant side effects of probing with MMC after 9 months of follow-up.

Our study showed that the patency rate of probing with MMC was significantly better than probing with normal saline throughout the study period.

5. Conclusion

The current study concluded that PANDO is a disease of middle age with no predilection for any gender. Epiphora is the most common presenting symptom with syringing and diagnostic probing confirming presence of NLDO.

Probing is a safe alternative to other surgical treatment to treat the condition. Probing with adjunctive MMC not only avoids cutaneous scarring as in DCR but also preserves the functional pump mechanism of tearing by maintaining the integrity of the orbicularis muscle and medial palpebral ligaments.

In conclusion, the result of this study demonstrate that MMC, at low concentrations (0.2 mg/ml), used as an adjunct for nasolacrimal duct probing, can improve both objective and subjective outcomes without imposing significant additional risk.

6. References

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