Probing and syringing with 3% Solution of NaCl and/or 0.2 mg/ml Mitomycin-C in Nasolacrimal Duct Obstruction Patients

Raveewan Choontanom MD*

To submit this paper as part of a MSc thesis at the Chulalongkorn University
** Department of Ophthalmology, Phramongkutklao College of Medicine, Bangkok, Thailand*

Objective: *To compare the efficacy of lacrimal probing and syringing among 3% solution of Sodium Chloride and/or 0.2 mg/ml Mitomycin-C as an adjunctive medication.*
Design: *A prospective, randomized, 2 by 2 factorial design study.*
Material and Method: *Forty-eight of nasolacrimal duct obstruction patients with epiphora symptom were randomly assigned to receive either Normal Saline Solution or 3% solution of Sodium Chloride or 0.2 mg/ml Mitomycin-C solution or combined 3% solution of Sodium Chloride with 0.2 mg/ml Mitomycin-C solution, during office probing and syringing. The intervention was performed repeatedly at week 0, weeks 2 and 4. An assessment of epiphora with Visual Analogue Scale were evaluated at week 0, weeks 2, 4, 8 and 12.*
Results: *Probing and syringing was successfully reducing epiphora symptom. Mitomycin-C group showed a significant reduction in mean difference of Visual Analogue Scale score compared with Normal Saline Solution group (2.85, 95% CI: 1.164-4.536, $p < 0.001$) and 3% Sodium Chloride group (2.175, 95% CI: 0.489-3.861, $p < 0.01$). No complication or adverse event was found.*
Conclusion: *0.2 mg/ml Mitomycin-C solution of was the most effective medication for office probing and syringing in reducing epiphora symptom in nasolacrimal duct obstruction patients.*

Keywords: *Nasolacrimal duct obstruction, Probing, Syringing, NaCl 3%, Mitomycin-C*

J Med Assoc Thai 2010; 93 (Suppl. 6): S197-S202
Full text. e-Journal: *http://www.mat.or.th/journal*

Epiphora or tearing is a common problem, about 33% of the complaints, in everyday of ophthalmological practice[1], which mainly caused by lacrimal drainage system obstruction. Primary acquired nasolacrimal duct obstruction (NLDO) is caused by a localized inflammation and connective tissue fibrosis, which leads to the occlusion of the nasolacrimal duct, based on histopathologic examination of patients whom underwent dacryocystorhinostomy (DCR)[2,3], which differed from congenital nasolacrimal duct obstruction caused by a membranous block of the valve of Hasner.

Recently, the conventional treatment for NLDO is lacrimal surgery, external or endoscopic DCR, which is generally recommended in case of previous dacryocystitis. The best way of management in NLDO with evidence of no previous infection or dacryocystitis is thus somewhat controversial. Lacrimal probing has been used as an initial procedure in acquired NLDO, results of which were varied from 52-82%[4,5]. Those unfavorable outcomes were explained by further restenosis from introducing trauma to the nasolacrimal duct that lead to a fibrotic or a scar formation and also another pathogenesis of the obstruction, such as blockage of lacrimal lithiasis and accumulation of mucus debris which found reflux from canaliculus by compression at the lacrimal sac region.

Mitomycin-C (MMC), the chemotherapeutic agent, has a potent inhibition of fibroblast proliferation which used in prevention of closure of the osteotomy site in DCR[6,7]. Its efficacy of probing the nasolacrimal duct with MMC has been reported in which shown a single probing yielded a patency rate of 89% and after repeating procedure the overall patency rate was 94%[8].

Correspondence to:
Choontanom R, Department of Ophthalmology, Phramongkutklao College of Medicine, 315 Rajvithi Rd, Rajathevi, Bangkok 10400, Thailand.
Phone: 0-2354-7600
E-mail: ravee_choon@yahoo.com

3% Sodium Chloride (3% NaCl) solution, the hypertonic saline solution, which is known as a mucolytic agent for hypersecretory airway disease, its action could decrease the adhesiveness between surface epithelium and mucus debris and could enhance the mucociliary function[9]. Even though, there is no published data of 3% NaCl usage in treatment of NLDO. Theoretically, 3% NaCl could probably be useful in case of mucus blockage in NLDO.

Material and Method

This was a prospective, randomized, 2 by 2 factorial design study conducted between March 1, 2009 and February 28, 2010 at Eye Out Patient Department in Phramongkutklao Hospital, Bangkok, Thailand. Approval from the Royal Thai Army Medical Department, Institutional Review Board and written consent from all participants were obtained.

Patients with age over 18 years old who voluntarily came to the clinic with complaints of epiphora with abnormal drainage of tear outflow caused by any structural obstruction of lacrimal passage in the presence of a sac washout with some degree of reflux from the canaliculus and the presence some degree of irrigating fluid in nasal/oropharyngeal cavity by syringing were recruited to the present study. Any secondary causes of epiphora, previous periorbital and lacrimal surgery, previous orbital radiation, history of congenital obstruction of lacrimal system, history of trauma with facial fracture, history of allergic reaction to Sodium Chloride or Mitomycin-C, pregnancy and lactation would be excluded.

An allocation sequence was concealed within opaque sealed envelopes with labeled number. A block randomization (block of 4) for four treatment groups was used. An assignment of 4 groups was double-blinded to the participants and the outcome assessor. The treatment was not identified on the clinical form but was instead identified by code numbers, which were translated only at the end of the study.

Forty-eight of nasolacrimal duct obstruction patients with eiphora symptom were enrolled, the participants were assigned to receive either Normal Saline Solution (NSS) as a control or 3% solution of Sodium Chloride (3% NaCl) or 0.2 mg/ml Mitomycin-C solution (MMC) or combined 3% solution of Sodium Chloride with 0.2 mg/ml Mitomycin-C solution (MMC + NaCl), during office probing and syringing. 3% Sodium Chloride solution prepared from 3 gm Sodium Chloride powder with 100 ml of sterile water for injection. Concentrations of 0.2 mg/ml Mitomycin-C solution prepared from a powder preparation for injection (Kyowa, Tokyo, Japan) by mixed a 2-mg vial with 10 ml of sterile water for injection.

After signing an informed consent, participants had to complete a base line evaluation form and rated the Visual analogue scale (VAS) from 0-10 on the following 7 aspects, which were summed and calculated for "mean" score.

1. General epiphora symptoms
2. Ocular discomfort
3. Interfered vision
4. Difficulty with reading
5. Difficulty with driving or going out
6. Working disturbance
7. Mood disturbance

At week 0, weeks 2 and weeks 4, participants were probed and pre-syringed nasolacrimal duct with 1.0 ml of NSS, and afterward 3 times of 1.0 ml for a randomized adjunctive solution, which was pre-coded and concealed. A 1.0 ml of NSS would be syringed again at the end of syringing. Participants were asked not to swallow the solution and water for gargling was provided. Water irrigation of external ocular area thoroughly was followed after finish treatment. All participants were prescribed steroid eye-drop and oral antibiotics for 10 day (reducing inflammation and prevention of introducing infection from probing) after each visit for probing and syringing and were allowed to use artificial tear eye-drop until complete study.

The VAS score was reassessed at weeks 2, weeks 4, weeks 8 and weeks 12. Any subject missing more than 2 times follow-up was removed from the analysis.

Statistical analysis

All data were collected, coded, and analyzed by using SPSS software (SPSS® version 11.5) and STATA software (STATA® version 10). Continuous variables were compared with the independent Student's t-test, whereas the Chi-square test was used to compare the categorical data between groups. Generalized Estimating Equation (GEE) and repeated measure ANOVA statistic were used to analyze the outcome between each visit. The p-value < 0.05 was considered statistically significant.

Results

There were 34 (70.8%) females and 14 (29.2%) males, aged 64.7 (SD 7.4) years with a history of epiphora for 6.63 (SD 2.12) months. No participant dropped out from the study. There were no significant differ-

ences between groups regarding mean age, gender, affected side of obstruction, mean duration of epiphora symptom, evidence of reflux per compression at lacrimal sac by examination, underlying of systemic diseases, smoking habits and allergic history (Table 1).

At week 0, there was no significant difference of mean Visual Analogue Scale (VAS) scores among 4 groups ($p = 0.959$). After one visit of probing and syringing, mean VAS scores showed statistically significant change within each group and between groups over the followed-up period ($p < 0.001$) (Table 2).

Fig.1 demonstrates a markedly reduction of VAS score in MMC group at weeks 2 and during follow-up period compared with other groups. MMC group showed the most changing in mean difference of VAS scores among 4 groups at each followed-up period which compared with the mean VAS scores at week 0 (Table 3).

In Table 4 demonstrates that the mean difference of VAS score was significant reduction in MMC group compared with NSS group (2.850, 95% CI: 1.164-4.536, $p < 0.001$) and 3% NaCl group (2.175, 95% CI: 0.499-3.861, $p < 0.01$). There was no statistical significance of reduction in mean difference of VAS score compared MMC group with MMC + NaCl group (1.623, 95% CI: -0.063-3.309, $p = 0.06$).

When NSS group was analyzed as a control, the odds of mean difference of VAS scores changing

Table 1. Baseline characteristics of the four groups

		NSS (n = 12)	MMC (n = 12)	3% NaCl (n = 12)	MMC+NaCl (n = 12)	p-value
Age*	(year)	64.58 ± 7.59	63.83 ± 10.39	65.17 ± 5.65	65.08 ± 5.96	0.97
Gender	male	1 (8.3)	5 (41.7)	5 (41.7)	3 (25)	0.22
	female	11 (91.7)	7 (58.3)	7 (58.3)	9 (75)	
Side	right	6 (50)	7 (58.3)	7 (58.3)	7 (58.3)	0.97
	left	6 (50)	5 (41.7)	5 (41.7)	5 (41.7)	
Duration of Epiphora*	(month)	7 ± 3.05	7.08 ± 1.62	6.33 ± 1.78	6.08 ± 1.83	0.60
Reflux per Compression	no	7 (58.3)	7 (58.3)	5 (41.7)	8 (66.7)	0.66
	yes	5 (41.7)	5 (41.7)	7 (58.3)	4 (33.3)	
Systemic Disease	no	3 (25)	4 (33.3)	3 (25)	8 (66.7)	0.11
	yes	9 (75)	8 (66.7)	9 (75)	4 (33.3)	
Smoke	no	12 (100)	12 (100)	12 (100)	12 (100)	-
Allergy	no	10 (83.3)	10 (83.3)	10 (83.3)	10 (83.3)	1.00
	yes	2 (16.7)	2 (16.7)	2 (16.7)	2 (16.7)	

* Mean ± SD

NSS = Normal Saline Solution. MMC = 0.2 mg/ml Mitomycin-C solution. 3% NaCl = 3% solution of Sodium Chloride. MMC + NaCl = combined 0.2 mg/ml Mitomycin-C solution with 3% solution of Sodium Chloride.

Table 2. Mean Visual Analogue Scale scores

	NSS (mean ± sd)	MMC (mean ± sd)	3% NaCl (mean ± sd)	MMC + NaCl (mean ± sd)	p-value
week 0	6.80 ± 1.72	7.17 ± 1.62	7.02 ± 1.33	6.90 ± 2.12	0.959
weeks 2	4.33 ± 2.17	0.50 ± 0.52	4.54 ± 1.25	4.35 ± 1.95	< 0.001
weeks 4	3.60 ± 1.91	0.70 ± 0.71	2.57 ± 1.68	1.85 ± 1.43	< 0.001
weeks 8	4.20 ± 2.19	0.43 ± 0.65	2.94 ± 1.67	2.13 ± 1.52	< 0.001
weeks 12	4.71 ± 2.45	0.59 ± 0.64	3.20 ± 1.71	2.28 ± 1.61	< 0.001
p-value	< 0.001	< 0.001	< 0.001	< 0.001	

Table 3. Comparison of mean difference of Visual Analogue Scale scores

	NSS	p-value	MMC	p-value	3%NaCl	p-value	MMC + NaCl	p-value
weeks 2*	2.467	0.001	6.667	< 0.001	2.475	0.001	2.550	< 0.001
weeks 4*	3.200	< 0.001	6.467	< 0.001	4.450	< 0.001	5.050	< 0.001
weeks 8*	2.600	< 0.001	6.733	< 0.001	4.075	< 0.001	4.767	< 0.001
weeks 12*	2.092	0.002	6.575	< 0.001	3.817	< 0.001	4.625	< 0.001

*week 0 = baseline

Table 4. Comparison of mean difference of reduction in Visual Analogue Scale scores

Group Mean Difference	Std. Error (VAS)	95% CI	p-value	
NSS vs. MMC	2.850	0.610	1.164-4.536	< 0.001
3% NaCl	0.675	0.610	-1.011-2.361	1.000
MMC + NaCl	1.227	0.610	-0.459 - 2.913	0.303
MMC vs. NSS	-2.850	0.610	-4.536--1.164	< 0.001
3% NaCl	-2.175	0.610	-3.861--0.489	0.005
MMC + NaCl	-1.623	0.610	-3.309-0.063	0.065
3% NaCl vs. NSS	-0.675	0.610	-2.361-1.011	1.000
MMC	2.175	0.610	0.489-3.861	0.005
MMC + NaCl	0.552	0.610	-1.134-2.238	1.000
MMC + NaCl vs. NSS	-1.227	0.610	-2.913-0.459	0.303
MMC	1.623	0.610	-0.063-3.309	0.065
3% NaCl	-0.552	0.610	-2.238-1.134	1.000

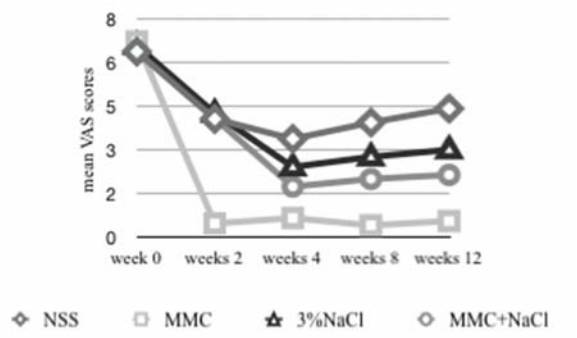

Fig. 1 Mean Visual Analogue Scale scores during follow-up periods, VAS = Visual Analogue Scale, The curves were constructed by plotting the mean VAS score at different points of time

was significantly 2.6 times greater in MMC group than in NSS group (OR -2.605: 95% CI -3.866- -1.343, p < 0.001). There was no statistical significance of mean difference of changing in mean VAS scores in 3%NaCl group (OR -0.668: 95%CI -1.929 - 0.594, p = 0.300) and MMC+NaCl group (OR -1.212: 95% CI -2.473 - 0.050, p = 0.060) (Table 5).

Discussion

The presented factorial 2 by 2 design study showed the efficacy of treatment which compared the outcome among different interested adjunctive medication groups, 0.2 mg/ml Mitomycin-C solution (MMC), 3% Sodium Chloride solution (3% NaCl) and, and also clarified that there was no interactive effect of a combination of both solution occurred, which based on Normal saline solution (NSS) as a control. Clinical efficacy was assessed on bases of epiphora with associated symptoms over the entire period of treatment (at week 0, weeks 2 and weeks 4) and the prolongation of treatment effect after treatment discontinuation (at weeks 8 and weeks 12).

The present study showed the reduction in Visual Analogue Scale (VAS) scores in all groups of treatment, but the MMC group proved to be the most effective medication after single probing and syringing. At the followed up periods of weeks 8 and weeks

Table 5. Changing of means difference of mean Visual Analogue Scale scores

Group*	OR	Std Error	95% CI	p-value
MMC	-2.605	0.644	-3.866 - -1.343	< 0.001
3%NaCl	-0.668	0.644	-1.929 - 0.594	0.300
MMC+NaCl	-1.212	0.644	-2.473 - 0.050	0.060

*NSS = control

12 after 3 times of probing and syringing, the mean VAS scores were slightly increased except in MMC group.

The safety and the adverse side effect of MMC usage has been considered by the author, for this particular reason the lowest concentration of 0.2 mg/ml has been selected, which been proved to be the safest[10] and effective[8,11,12] concentration.

Even though, there was reported that hypertonic saline solution could osmotically draw water into surface and improving mucus clearance in airway disease[13] and also an improvement in mucociliary transit time seen in hypertonic saline nasal irrigation comparing with normal saline nasal irrigation[14]. In the presented study, the treatment of NLDO with probing and syringing in 3% NaCl group shown a reduction in mean VAS score but no statistical difference compare with NSS group.

There were several limitations of the present study. Firstly, epiphora is a subjective symptom and the outcome measurement was a grading of the symptom used Visual Analogue Scale so some unreliability or bias may be occurred. Secondly, the author reported a short term followed-up period (12 weeks) which the long term of the efficacy be questioned, a further follow-up evaluation is suggested. Thirdly, office probing and syringing required experience and proper techniques to minimize trauma to the nasolacrimal duct which could lead to re-inflammation or introduce some degree of infection caused re-stenosis or dacryocystitis.

In conclusion, the present study addressed the efficacy of the intervention of office probing and syringing in treatment of nasolacrimal duct obstruction patients with epiphora. An adjunctive medication of 0.2 mg/ml Mitomycin-C solution is an effective medication to reduce an epiphora symptom. However, office probing and syringing results some degree of discomfort, even this intervention done after application of topical anesthetic eye drops. Therefore, counseling, explanation of the intervention and reassurance are strongly suggested.

Conclusion

Mitomycin-C with concentration of 0.2 mg/ml was the most effective medication in adjunction to office probing and syringing for reducing epiphora symptom in nasolacrimal duct obstruction patients.

Acknowledgements

The researcher wish to thank Pramongkutklao College of Medicine for the financial support of this research and a special thanks to Miss. Supak Cae-ngow for her helpfulness in the statistical analysis. Finally, we would like to express a deep gratitude to Dr. Kittisak Kulvichit for his attention and helpful suggestion.

References

1. Gillissen JPA, Van Noort B. Epiphora, how to solve a common problem? Orbit 1990; 9: 293-4.
2. Linberg JV, McCormick SA. Primary acquired nasolacrimal duct obstruction. A clinicopathologic report and biopsy technique. Ophthalmology 1986; 93: 1055-63.
3. Tucker N, Chow D, Stockl F, Codere F, Burnier M. Clinically suspected primary acquired nasolacrimal duct obstruction: clinicopathologic review of 150 patients. Ophthalmology 1997; 104: 1882-6.
4. Bartley GB. Acquired lacrimal drainage obstruction: an etiologic classification system, case reports, and a review of the literature. Part 1. Ophthal Plast Reconstr Surg 1992; 8: 237-42.
5. Bell TA. An investigation into the efficacy of probing the nasolacrimal duct as a treatment for epiphora in adults. Trans Ophthalmol Soc U K 1986; 105(Pt 4): 494-7.
6. Liao SL, Kao SC, Tseng JH, Chen MS, Hou PK. Results of intraoperative mitomycin C application in dacryocystorhinostomy. Br J Ophthalmol 2000; 84: 903-6.
7. Camara JG, Bengzon AU, Henson RD. The safety

and efficacy of mitomycin C in endonasal endoscopic laser-assisted dacryocystorhinostomy. Ophthal Plast Reconstr Surg 2000; 16: 114-8.
8. Tsai CC, Kau HC, Kao SC, Hsu WM, Liu JH. Efficacy of probing the nasolacrimal duct with adjunctive Mitomycin-C for epiphora in adults. Ophthalmology 2002; 109: 172-4.
9. Middleton PG, Pollard KA, Wheatley JR. Hypertonic saline alters ion transport across the human airway epithelium. Eur Respir J 2001; 17: 195-9.
10. Rubinfeld RS, Pfister RR, Stein RM, Foster CS, Martin NF, Stoleru S, et al. Serious complications of topical mitomycin-C after pterygium surgery. Ophthalmology 1992; 99: 1647-54.
11. Kim KR, Song HY, Shin JH, Kim JH, Choi EK, Lee YJ. Efficacy of mitomycin C irrigation after removal of an occluded nasolacrimal stent. J Vasc Interv Radiol 2007; 18: 519-25.
12. Kim KR, Song HY, Shin JH, Kim JH, Choi EK, Yang ZQ, et al. Efficacy of mitomycin-C irrigation after balloon dacryocystoplasty. J Vasc Interv Radiol 2007; 18: 757-62.
13. Boucher RC. Evidence for airway surface dehydration as the initiating event in CF airway disease. J Intern Med 2007; 261: 5-16.
14. Talbot AR, Herr TM, Parsons DS. Mucociliary clearance and buffered hypertonic saline solution. Laryngoscope 1997; 107: 500-3.

การแยงและล้างท่อน้ำตาด้วยสารละลายน้ำเกลือ 3 เปอร์เซ็นต์ และ/หรือ สารไมโตมัยซิน-ซี 0.2 มก./มล. ในผู้ป่วยท่อน้ำตาตัน

รวีวรรณ ชุนถนอม

วัตถุประสงค์*: เพื่อประเมินประสิทธิผลของการแยงและล้างท่อน้ำตาด้วยสารละลายน้ำเกลือ 3 เปอร์เซ็นต์ และ/หรือ สารไมโตมัยซิน-ซี 0.2 มก./มล.*

ชนิดของการศึกษา*: ชนิด 2 คูณ 2 แฟคทอเรียล แบบไปข้างหน้าด้วยวิธีการสุ่ม*

วัสดุและวิธีการ*: ผู้ป่วยท่อทางเดินน้ำตาอุดตัน 48 คน ที่มีภาวะตาแฉะน้ำตาไหล จะได้รับการสุ่มให้ได้รับการแยงและล้างท่อน้ำตาด้วยสารละลายน้ำเกลือธรรมดา หรือสารละลายน้ำเกลือ 3 เปอร์เซนต์ หรือสารละลายไมโตมัยซินซี 0.2 มก./มล. หรือสารละลายผสมระหว่างน้ำเกลือ 3 เปอร์เซนต์ และไมโตมัยซินซี 0.2 มก./มล. การแยงและล้างท่อน้ำตาจะกระทำในสัปดาห์แรก สัปดาห์ที่ 2 และสัปดาห์ที่ 4 จะมีการประเมินภาวะตาแฉะน้ำตาไหลโดยใช้เครื่องมือ visual analogue scale ในสัปดาห์แรก สัปดาห์ที่ 2, 4, 8 และ 12*

ผลการศึกษา*: การแยงและล้างท่อน้ำตาสามารถลดอาการตาแฉะน้ำตาไหลได้ สำหรับกลุ่มผู้ป่วยที่ได้รับการแยงและล้างท่อน้ำตาด้วยสารไมโตมัยซิน-ซี มีค่าเฉลี่ยที่ลดลงของ visual analogue scale อย่างมีนัยสำคัญทางสถิติเมื่อเทียบกับกลุ่มที่ได้รับสารละลายน้ำเกลือธรรมดา (2.85, 95% CI: 1.164-4.536, p < 0.001) และกลุ่มที่ได้รับสารละลายน้ำเกลือ 3 เปอร์เซนต์ (2.175, 95% CI: 0.489-3.861, p < 0.01) โดยในการศึกษาไม่พบภาวะแทรกซ้อนหรืออาการไม่พึงประสงค์ใด ๆ*

สรุป*: การแยงและล้างท่อน้ำตาด้วยสารละลาย ไมโตมัยซิน-ซี 0.2 มก./มล. มีประสิทธิผลมากที่สุดในการลดอาการตาแฉะน้ำตาไหลในผู้ป่วยที่มีท่อทางเดินน้ำตาอุดตัน*