Clinical Trial/Experimental Study

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Tobramycin/dexamethasone eye drops as a better choice for lacrimal duct probing in persistent congenital nasolacrimal duct obstruction

A consort study

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Abstract

Background: Congenital nasolacrimal duct obstruction (CNLDO) is common and. lacrimal duct probing is the major treatment. But persistent CNLDO in older children makes the success rate rapidly decreased due to long-term chronic inflammation. To improve the success rate, probing combined with tobramycin/dexamethasone ointment is considered effective. But in practice, we found a lot of problems in using the ointment. So we tried tobramycin/dexamethasone eye drops as a replacement. The results is surprising, so we hope to do some further research in order to prove it is worth to clinical application.

Objective: To evaluate the effect of lacrimal duct probing combined with tobramycin/dexamethasone eye drops or ointment on persistent CNLDO in children older than 1-year-old.

Methods: This randomized controlled study included 409 subjects (496 eyes) older than 1-year-old with persistent CNLDO in southwest China, and classified into 3 groups: 96 cases (123 eyes) were the tobramycin/dexamethasone eye drops group (drops group), 88 cases (104 eyes) were the tobramycin/dexamethasone ointment group (ointment group), and 225 cases (269 eyes) were control group which probing with normal saline (NS group). The data of age, sex, and laterality were analyzed through pairwise comparison. Then the 3 groups were divided into 2 subgroups by age, 12 to 24 months and 25 to 36 months. The surgical findings and success rate in two subgroups were compared.

Results: The success rates in the tobramycin/dexamethasone eye drops group in both 2 age subgroups were significantly higher than that in the ointment group and NS group ($P < .05$).

Conclusions: Probing combined with tobramycin/dexamethasone eye drops was effective and easy-to-perform in the clinic, and it may be a better choice for persistent CNLDO.

Abbreviations: CNLDO = congenital nasolacrimal duct obstruction, NS group = normal saline.

Keywords: congenital nasolacrimal duct obstruction, lacrimal duct probing, tobramycin/dexamethasone

1. Introduction

Congenital nasolacrimal duct obstruction (CNLDO) affects approximately 6% to 12.5% of newborns.[1] Over 85% of cases resolve spontaneously during the first year of life,[2] so proper treatments may be ignored and delayed by their parents. Persistent CNLDO makes the condition complex due to long-term chronic inflammation.[3] Lacrimal duct probing is one of the major treatments for CNLDO with a high success rate.[4] Many studies have shown that the success rate of probing in simple CNLDO is significantly higher than that in complex CNLDO. Kushner reported 100% success rate of probing in simple obstruction and 36% success rate in complex obstruction.[5] Therefore, although the timing of probing for CNLDO has been debated, probing for CNLDO is particularly recommended for avoiding long-term chronic inflammation.[6]

Lacrimal duct probing combined with an infusion of tobramycin/dexamethasone ointment is considered effective.[7–9] But, the use of ointment injection combined with probing still remains an uncommon procedure and is not recommended for lacrimal duct probing surgery in many countries. In our previous practice, we found a lot of problems of ointment during probing. Before the operation, the ointments must be prepared via a hot melt process. If the ointment solidified during the cooling process, the probe may easily become blocked, thus making the operation difficult and inconvenient.

Thus we tried using tobramycin/dexamethasone suspension instead of tobramycin/dexamethasone eye ointment. Accidentally, the result made us excited, although the residence time of the drug is shorter, the success rate seemed improved, especially for

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older children. Therefore, an experiment was designed, to compare tobramycin/dexamethasone eye drops suspension to ointment on the success rate of the probing, in order to find proper therapy for clinical application.

2. Methods

2.1. Inclusion criteria and grouping situations

This research recruited 409 patients (496 eyes) ranging from 12 to 36 months diagnosed with persistent CNLDO from July 2015 to February 2017 in the Children's Hospital of Chongqing Medical University, Chongqing, China. The inclusion criterion included age older than 1-year-old, diagnosed with CNLDO, and regular lacrimal sac massage was ineffective. The diagnosis of CNLDO depended upon the history of epiphora, mucopurulent discharge after birth, and confirmation via the sac regurgitation test.[10,11] Children with a history of previous probing or associated ocular disease were excluded from this study. According the success rate of literature, our sample size was sufficient to reach over 95% power value at the 5% significance level.

They were divided into 3 groups randomly: 96 cases (123 eyes) were the tobramycin/dexamethasone eye drops group (drops group), 88 cases (104 eyes) were the tobramycin/dexamethasone ointment group (ointment group), 225 cases (269 eyes) were control group which probing with normal saline (NS group). The data of age, sex, and laterality in these 3 groups were analyzed through pairwise comparison. Then the 3 groups were divided into 2 subgroups by age, 12 to 24 months and 25 to 36 months. The surgical findings and success rate in 2 subgroups were compared. All subjects' parents or guardians gave their written informed consent for this operation. All procedures followed the tenets of the Declaration of Helsinki.

2.2. Preoperative preparation and probing procedure

Before probing, all subjects received proper lacrimal massage, 0.3% tobramycin eye drops (Tobrex, Alcon, Fort Worth) 3 times a day and continual high-pressure irrigation of the lacrimal system with physiological saline weekly for a total of 5 to 6 times until there was no mucopurulent discharge.

Probing was performed by the same pediatric ophthalmologist under brief general anesthesia. A syringe of tobramycin/dexamethasone eye drops suspension (5 mL of tobramycin 3 mg/mL and dexamethasone 1 mg/mL) or tobramycin/dexamethasone eye ointment (5 mL of tobramycin 0.3% and dexamethasone 0.1%) or NS was connected to the puncture needle. Ointments were prepared via the hot melt process before use. After the upper lacrimal punctum was slightly expanded, a 23-gauge lacrimal cannula was used for probing, which measures 0.25 mm at the aspiration port. The size was determined according to the diameter of the horizontal canaliculus for cases and stiffness for operation. The probe was advanced until it touched the wall of the lacrimal fossa through the canaliculus. Then the probe was gently rotated downward to the nasolacrimal duct until the obstruction could be felt. At the same time, 0.5 mL of drug or saline was forcefully infilled into the lacrimal passage as the needle was drawn out.

The situation of obstruction was recorded the after operation. Simple obstruction was defined as a membranous or complex blockage. Complex obstruction was defined as inflammatory obstruction, meaning that the probe encountered more resistance in addition to the presence of mingled pus and blood through the probe. Ointments were prepared via the hot melt process before use. Finally, a syringe of TobraDex eye drops suspension (5 mL of tobramycin 3 mg/mL and dexamethasone 1 mg/mL) or TobraDex eye ointment (5 mL of tobramycin 0.3% and dexamethasone 0.1%) was connected to the puncture needle, and 0.4 to 0.5 mL of drug was forcefully infilled into the lacrimal passage as the needle was drawn out.

2.3. Post management after probing

Postoperatively, the children's parents were informed to stop lacrimal sac massage in order to maintain the drug's efficacy. Tobramycin eye drops were used 3 times a day for 1 week. Patients were re-evaluated at regular intervals of 1 week, 1 month, and 3 months. Successful probing was considered as complete resolution of epiphora and discharge over 3 months of follow-up.

No intraoperative complication was found in the procedure.

3. Statistical analysis

SPSS software (version 21.0) was used for all statistical calculations (SPSS, Inc, Chicago, IL). Mean ages were stated as mean ± standard deviation and analyzed by ANOVA. Chi-square tests (χ^2 test) were conducted to compare the frequency count in different groups. The sex, laterality, surgical findings, and primary probing success rate in three groups were compared via the χ^2 test; a P-value $< .05$ was regarded as statistically significant.

4. Ethics approval

The study was approved by the Ethics Committee of the Children's Hospital of Chongqing Medical University, Chongqing, China (Permit No. 090/2016). Written informed consent was obtained from the parents of each subject.

5. Results

5.1. Clinical characteristic of subjects in the 3 groups

There were no statistical differences in age, sex, and laterality among these 3 groups using pairwise comparison (Table 1). Forty-seven (53.4%) patients were male and 41 (46.6%) patients were female in the ointment group, 50 (52.1%) patients were male and 46 (47.9%) patients were female in the drops group, while 114 (50.7%) patients were male and 111 (49.3%) patients were female in the NS group. The average age was 18.54 ± 6.15 months, 18.10 ± 5.79 months, and 17.96 ± 6.05 months for drops group, ointment group, and NS group, respectively. In the drops group, 69 subjects (71.9%) were unilateral CNLDO, whereas 72 subjects (81.8%) were unilateral in the ointment group and 181 (80.4%) subjects were unilateral CNLDO. Statistical analyses were also performed for different ages subgroups (12–24 months and 25–36 months), but no statistical differences were found (data not shown).

5.2. Surgical findings of the 3 groups

There were no statistical differences in the surgical findings, including nasal bleeding and purulent discharge among the three groups in both subgroups (12–24 months and 24 to 36 months; $P > .05$). There was also no statistical difference in the surgical findings between the age 12 to 24 months subgroup and the 24 to 36 months subgroup in the 3 groups ($P > .05$). Data are presented in Table 2.

Table 1

Clinical characteristics of the 3 groups.

		Ointment group (n = 88 subjects)	Drops group (n = 96 subjects)	NS* group (n = 225 subjects)	Significance
Age†	Months	18.10 ± 5.79	18.54 ± 6.15	17.96 ± 6.05	NS†
Sex	Male (%)	47 (53.4%)	50 (52.1%)	114 (50.7%)	NS†
	Female (%)	41 (46.6%)	46 (47.9%)	111 (49.3%)	
Laterality	Unilateral (%)	72 (81.8%)	69 (71.9%)	181 (80.4%)	NS†
	Bilateral (%)	16 (18.2%)	27 (28.1%)	44 (19.6%)	

*NS: normal saline.
†NS: no significance.

5.3. Comparison of success rate among the 3 groups

5.3.1. Success rate among the 3 groups in 2 age subgroups.

The results showed that the general surgical success rate was 85.4% in the drops group, which was significantly superior to the 66.3% in the ointment group and 66.2% in the NS group ($P = .001$, $P = 8.3E{-}5$, respectively). For children aged 12 to 24 months old, the success rate in the drops group was 90.3%, compared with 74.2% in the ointment group and 70.4% in the NS group ($P = .014$, $P = .001$, respectively). For children aged 25 to 36 months years old, the success rate in the drops group was 78.4%, compared with 54.8% in the ointment group and 56.2% in the NS group ($P = .015$, $P = .01$, respectively). Data were presented in Table 3.

5.3.2. Surgical success rate between age subgroups in both ointment and drops group.

The surgical success rates between the age 12 to 24 months subgroup and the 25 to 36 months subgroup were statistically different in the ointment group and NS group, but there was no statistical difference in the drops group (Fig. 1). In ointment group, the success rate was 74.2% in 12 to 24 months subgroup, while 54.8% in 25 to 36 months subgroup ($P = .04$). In the NS group, the success rate of 12 to 24 months subgroup was 70.4% compared with 56.2% of 25 to 36 months subgroup ($P = .03$).

6. Discussion

This study included 409 subjects (496 eyes) for the evaluation of the effect of lacrimal duct probing in combination with tobramycin/dexamethasone eye drops or ointment in children older than 1 year with persistent CNLDO. The results showed that the general surgical success rate was over 85% in the tobramycin/dexamethasone eye drops group, which was significantly superior to the success rate in the ointment group and NS group. The success rate decreased with age, but the difference was not statistically significant in the eye drops group.

Many researchers have reported higher failure rates if probing is delayed.[2,12] In our experiment, the success rates obviously decreased with increased age in both ointment group and NS group, but there was no significant difference in the eye drops group, although seemed slightly decreased with growing age. This might be due to other risk factors rather than age, in spite of age was considered as an important risk factor in CNLDO according to many studies.[3,13,14] However, other research has reported that age is not a vital risk factor for probing.[6,15,16] Rajat Maheshwari has pointed out that in older children the high success rate of probing in simple obstruction means age alone is probably not the deciding factor for the success of probing.[10] Kim et al observed the efficiency of antibiotic irrigation for CNLDO and proposed that the success rate of probing decreases because of the fibrotic change caused by inflammation and scarring.[17] There are hypotheses that the higher failure rate in older children may be attributable to persistent inflammation and fibrosis of the lacrimal duct epithelium[18] or accumulation of obstruction, rendering the CNLDO complex.[19] Thus, inflammation may be the key risk factor for success in probing.

Both tobramycin/dexamethasone eye drops and eye ointment consists of 0.3% tobramycin and 0.1% dexamethasone.[20] Tobramycin is an aminoglycoside antibiotic that has outstanding

Table 2

Surgical findings among 3 groups in 2 age subgroups.

Age, mo	Surgical findings		Ointment group	Drops group	NS* group	*P*
12–24			n = 62 eyes	n = 72 eyes	n = 189 eyes	
	Bleeding	Yes	29 (46.8%)	37 (51.4%)	90 (47.6%)	.83
		No	33 (53.2%)	35 (48.6%)	99 (52.4%)	
	Purulent discharge	Yes	51 (82.3%)	61 (84.7%)	160 (84.7%)	.90
		No	11 (17.7%)	11 (15.3%)	29 (15.3%)	
25–36			n = 42 eyes	n = 51 eyes	n = 80 eyes	
	Bleeding	Yes	26 (61.9%)	33 (64.7%)	45 (56.2%)	.61
		No	16 (38.1%)	18 (35.3%)	35 (43.8%)	
	Purulent discharge	Yes	35 (83.3%)	41 (80.4%)	67 (83.8%)	.88
		No	7 (16.7%)	10 (19.6%)	13 (16.3%)	
Total			n = 104 eyes	n = 123 eyes	n = 269 eyes	
	Bleeding	Yes	55 (52.9%)	70 (56.9%)	135 (50.2%)	.46
		No	49 (47.1%)	53 (43.1%)	134 (49.8%)	
	Purulent discharge	Yes	86 (82.7%)	102 (82.9%)	227 (84.4%)	.89
		No	18 (17.3%)	21 (17.1%)	42 (15.6%)	

The data were calculated by the number of eyes.
*NS: normal saline.

Table 3

Success rate of the 3 groups by age.

Age, mo	Probing result	Ointment group	Drops group	NS† group	P^{*}	P^{**}	P^{***}
12–24		n=62 eyes	n=72 eyes	n=189 eyes			
	Success (%)	46 (74.2%)	65 (90.3%)	133 (70.4%)	1.4E−2	.56	1.0E−3
	Failure (%)	16 (25.8%)	7 (9.7%)	56 (29.6%)			
25–36		n=42 eyes	n=51 eyes	n=80 eyes			
	Success (%)	23 (54.8%)	40 (78.4%)	45 (56.2%)	1.5E−2	.88	.01
	Failure (%)	19 (45.2%)	11 (21.6%)	35 (43.8%)			
Total		n=104 eyes	n=123 eyes	n=269 eyes			
	Success (%)	69 (66.3%)	105 (85.4%)	178 (66.2%)	1.0E−3	.97	8.3E−5
	Failure (%)	35 (33.7%)	18 (14.6%)	91 (33.8%)			

The data were calculated by the number of eyes.
†NS: normal saline.
*P: ointment group compared with drops group.
**P: ointment group compared with NS group.
***P: drops group compared with NS group.

antibacterial effects against *Pseudomonas*, *Staphylococcus aureus*, and many members of the *Enterobacteriaceae* family.[8] Dexamethasone is a corticoid which inhibits inflammation and the proliferation of fibroblasts after probing.[9] The compound drug composition and concentration of tobramycin/dexamethasone eye drops and eye ointment are the same. The only difference between them is that the base.[21] The base of ointment is white petrolatum, mineral oil, and lanolin.[21] Ointment is commonly used in ophthalmology because the base of petrolatum which could prolongs the drug residence time. Therefore, petrolatum-based tobramycin/dexamethasone ointment should theoretically prevent infection, reduce inflammation, lubricate the lacrimal passage, and increase drug delivery time combined with probing.[15,20]

Actually, if the ointment, which is in a base of white petrolatum, mineral oil, and lanolin, strays into other ocular tissue, may cause a serious reaction.[22,23] Wang et al observed inflammatory reactions, absorption, degradation, and histopathological changes of different eye-ointment substrates upon entering the subconjunctival tissues, and they found that the inflammation reaction of erythromycin eye ointment is the most serious; the degradation and absorption are the slowest; and the histopathological changes are the most severe. Thus, they recommended that this kind of ointment with a base of white petrolatum, mineral oil, and lanolin should not be used on the surface of wounds and in lacrimal duct probing surgery, The ointment can only be used for conjunctiva.[24] We hypothesize that the success rate of the ointment group decreased due to inflammation caused by the base components of the tobramycin/dexamethasone ointment. Further studies are needed to validate this hypothesis.

This was the first report, to our knowledge, on combining tobramycin/dexamethasone eye drops suspension with the primary probing procedure for persistent CNLDO in children older than 1 year. We found that tobramycin/dexamethasone eye drops performed better than an ointment and NS. And the eye drops group maintained a high success rate in both age subgroups (12–24 months and 25–36 months) and meantime higher than the other 2 groups with pairwise comparison. So, for children with persistent CNLDO especially older ones, we recommend tobramycin/dexamethasone eye drops for the probing.

However, there are still many problems requiring further research. For instance, it is worth to determine whether tobramycin/dexamethasone eye drops is also effective in the second probing or even multiple probing surgeries. Tobramycin/dexamethasone eye ointment contains a variety of components, and it is not certain which component play the major role in inflammatory response and fibrosis, further experiments are needed to identify this problem, and could improve the production process of eye ointment in the future. This study only recruited 409 subjects, an increased in the sample volume experiment will be needed to verify our results.

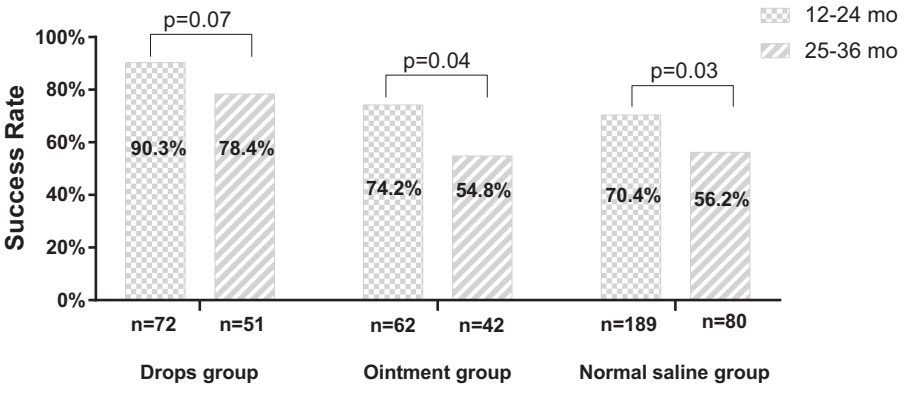

Figure 1. Success rate between the two age subgroups among the 3 groups. Statistical significance level: $P < .05$. The data were calculated by the number of eyes (n=eyes).

7. Conclusion

Probing combined with tobramycin/dexamethasone eye drops was effective and easy-to-perform in the clinic, and it may be a better choice for older children with persistent CNLDO. If the child is considered for lacrimal duct surgery, doctor can try the probing with tobramycin/dexamethasone eye drops first to improve the success rate.

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Author contributions

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Investigation: Xu Gao.
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