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Conjunctival bacterial flora in fellow eyes of patients less than 5 y/o with unilateral nasolacrimal obstruction and its changes after successful probing surgery

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ABSTRACT

Background: Congenital nasolacrimal duct obstruction (CNLDO) is one of the leading causes of epiphora in infants, in which antibiotics are usually used as a conservative therapy in the first year. *Objectives:* This study aimed to evaluate the conjunctival bacterial flora in fellow eyes of patients 1-5 years old with unilateral NLDO and its changes after successful probing surgery. *Methods:* This prospective case-control study was conducted on children between 1-5 years old with unilateral NLDO with successful probing surgery in 2021. Before probing procedure and postoperative sampling from the conjunctiva of the eyes continued weekly until the colony count became negative or normal. Positive culture (clinically significant growths), colony count, and detected bacteria types reported. *Results:* The positive culture of conjunctival bacteria was observed in 71 (73.96%) in the case group and 35 eyes (36.46%) in the control group (P<0.0001). Most bacterial species in the case and control groups were gram-positive (75.61% and 82.86%, respectively; P=0.181). The most common isolated microorganisms in both groups were *Staphylococcus epidermidis* (54.95% and 51.43%) and *Staphylococcus aureus* (16.9% and 21.43%). The mean normalization time of bacterial culture was 1.92±0.54 weeks (between 1-3 weeks). The time for normalization of cultured bacteria was significantly related to the initial colony count≥1000 and the presence of a silicone tube (P<0.0001). *Conclusions:* Present study shows that gram-positive organisms with the predominance of *Staphylococcus spp.* were the significant conjunctival bacterial flora in pediatrics with NLDO. These findings could be helpful for management and appropriate antibiotic selection for treating of NLDO in our region.

Keywords: Congenital nasolacrimal duct obstruction, Bacteriology, Lacrimal sac, Conjunctiva

1. INTRODUCTION

Background

Congenital Nasolacrimal Duct Obstruction (CNLDO) is a communal disease in infants and one of the leading causes of epiphora or watery eyes in infants (Świerczyńska et al., 2020; Vagge et al., 2018). Nasolacrimal duct obstruction usually occurs as a result of mechanical obstruction of Hasner's valve (located at the end of the nasolacrimal duct), which leads to blockage or retention of tear fluid in the lacrimal sac (Usha et al., 2006; Sathiamoorthi et al., 2019). Symptoms of NLDO include epiphora and suppuration, which can cause eczema, blepharitis, and eczematous dermatitis (Yang et al., 2022). Lacrimal duct obstruction is unilateral in most cases (about 80%) (Olitsky, 2014). NLDO occurs in 5 to 20% of normal infants and is typically non-emergent (Vagge et al., 2018; Bekmez et al., 2019). Tear sac secretions can affect the balance of the conjunctival flora. In the nasolacrimal duct obstruction condition, any bacteria types, even normal flora, can cause infection (Gerkowicz et al., 2005; Badhu et al., 2006).

Treatment methods for CNLDO include observation and follow-up, local antibiotic eye drops, massage, irrigation, and lacrimal canal probing. The decision on the type of treatment is made based on the natural history, kind of obstruction, and clinical manifestations (Vagge et al., 2018; Schellini et al., 2021). However, CNLDO patients recover spontaneously within the first year of birth (Kakizaki et al., 2008; Group PEDI, 2012). A conservative treatment for CNLDO-related infection in patients aged up to 12 months is the use of broad-spectrum antibiotic eye drops (Bekmez et al., 2019; Zheng et al., 2020). Due to the similarity of conjunctival bacterial flora in CNLDO patients with the average population, antibiotic eye drops may cause antibiotic resistance (Schellini et al., 2021; MacEwen et al., 1994).

Objective

Bacterial culture of lacrimal sac secretions is a standard clinical method to identify pathogenic bacteria that assist in treating patients. Comprehending the culture results can facilitate effective antimicrobial agent selection, reduce microbial load and purulent secretions, and prevent severe infectious complications (Usha et al., 2006; Yang et al., 2022). Since the frequency and types of bacterial species in CNLDO are different among ethnic populations Eslami et al., (2018), and there is a lack of information about the bacteriology of the obstructed lacrimal drainage system in children with CNLDO, this study aims to investigate the normal bacterial flora of the conjunctiva in children that have unilateral CNLDO.

2. METHODS

Participants and ethical considerations

The present study is a prospective experimental case-control study conducted in the Ophthalmology Clinic of Ahvaz Imam Khomeini Hospital patients in 2021. The children aged 1 to 5 years with unilateral nasolacrimal duct obstruction who did not consume any antibiotic and in their lacrimal probing met the criteria of no lacrimation and the test of the time it takes to clear the fluorescein dye solution from the patients' eyes; They participated in the study with the consent of their parents or guardians. Patients whose lacrimal probing was unsuccessful, had eye surgery in the last six months, had conjunctivitis, and had systemic or immunodeficiency diseases were excluded from the study. In all stages of this research, the Declaration of Helsinki guidelines and the principles of confidentiality of patients' information were met. The study was conducted after obtaining permission from the Research Council and approval of the Ethics Committee of Ahvaz University of Medical Sciences (code of ethics: IR.AJUMS.REC.1398.145).

Measurement of study sample size

Purposeful sampling used to select the study population. Based on previous studies Eshraghi et al., (2016), Owji & Khalili, (2009), the study sample size considering the confidence level of 95% ($\alpha = 0.05$), the power of 90% ($\beta = 0.1$), and using the mean comparison formula, the average of at least 76 people in each group calculated. But in the end, 96 people in each group included in the study to reduce the errors and comply with various aspects.

Case selection

A group of children aged 1-5 years with unilateral NLDO and successful lacrimal probing operation (case group) and a group of intact children without lacrimal duct obstruction (control group) were included in the study. The control group had entire, unharmed children referred to the ophthalmology clinic who were examined under anesthesia and selected after matching in terms of age and sex. NLDO was diagnosed based on clinical characteristics, purulent mucous secretions, and epiphora. When pressure

applied to the lacrimal sac, the discharge of mucoid or mucopurulent material observed from the punctum. Ninety-six children aged 1 to 5 years with unilateral NLDO underwent successful lacrimal probing (case group) and a group of intact children as a control group.

Sampling

All children sampled from the conjunctiva before lacrimal probing. For this purpose, the skin around the eyes and the edge of the eyelid was cleaned with sterile normal saline. Then, the lower eyelid stretched with a cotton swab to expose the lower fornix, and a conjunctival sample taken from the lower fornix from the nasal side, to the temporal side, without using local anesthesia. It avoided contact of the swab with the eyelid edge, then the swab placed in a sterile sample tube containing normal saline, and the samples sent to the laboratory (Department of Microbiology, Imam Khomeini Hospital, Ahvaz).

Bacterial culture

Conjunctival sampling performed in all children before lacrimal probing. First, the skin around the eyes and the eyelid edge cleaned with sterile normal saline. The inferior palpebra is stretched with a cotton swab to expose the lower fornix. Without local anesthesia, a conjunctival sample was taken from the inferior fornix from the nasal side to the temporal side by a sterilized swab. During sampling, the swab controlled from touching the eyelid edge. The swab placed in a sterile test tube containing normal saline. The swab sample immediately sent to the laboratory (Microbiology Unit of Imam Khomeini Hospital, Ahvaz). For bacterial growth evaluation, the samples first placed in Blood Agar and Eosin Methylene Blue Agar (EMB; Condalab Co., Madrid, Spain) media. Bacterial culture carried out at 37°C for 48 hours in a vacuum incubator (Behdad, Model 1008, Paish Goghel Bortar Co., Iran).

The growth of a single colony considered as a positive test. "The Disk diffusion" protocol published by Padtan Teb Co., Iran, used to check the results. In case of no growth of bacteria, the sample transferred to the thioglycolate medium and then recultured. Colonies counted by visual inspection and manual counting. Single colonies were selected and isolated to classify the bacterial strains through streaking or picking techniques on individual agar plates. These isolated colonies subjected to various biochemical tests with Gram staining (Taligene Pars Co., Iran), catalase test (Baharafshan Co., Iran), oxidase test (Baharafshan Co., Iran), and coagulase test (Baharafshan Co., Iran), to determine their characteristics and identify their species. After the successful completion of probing, these steps continued weekly until the culture result became negative or when the number of colonies was equal to the control group.

Statistical Analysis

SPSS (SPSS Inc, USA) version 25 used for statistical analysis. Mean, standard deviation and frequency used for quantitative descriptive data. An Independent t-test used to compare the average variables between two groups, Pearson's Chi-square test (or Fisher's exact) and correlation test used to determine the relationship between quantitative and qualitative variables, respectively. To check the alteration in the mean of the variables over time, Tukey's post hoc test and repeated measures analysis of variance used to compare the two-by-two means. The significant level considered 0.05 in the analysis.

3. RESULTS

Ninety-six children aged 1 to 5 years with unilateral NLDO underwent successful lacrimal probing (case group) and a group of intact children as a control group. In this study, silicone bulb used for 16 patients (21.05%), in whom average age was 2.86 ± 0.71 years. The essential characteristics and results of conjunctival bacterial culture in two groups present in (Table 1). Positive conjunctival bacterial culture observed in 71 (73.96%) of the patients in the case group and 35 (36.46%) in the control group (P<0.0001). Among these, one bacterial species observed in 63 cases (88.73%), and more than one bacterial species observed in 8 patients (11.27%) (P=0.094). Most bacterial species identified in both case and control groups were gram-positive (75.61% and 82.86%, respectively; P=0.181).

The differences in the statistical analysis in type of bacteria section (Table 1) observed which was due to our specific evaluation and focus on gram positive and negative species only, not other bacteria type classifications (Table 1). The types of bacteria detected in the positive conjunctival cultures of the studied children are presented in Table 2. The most common gram-positive species were *Staphylococcus epidermidis* and *Staphylococcus aureus*. The most common gram-negative species were *H. influenza* and *Klebsiella*. Based on the found results, there was no substantial difference between the bacterial flora of the conjunctiva in children aged 1-5 years with and without nasolacrimal duct obstruction (control group) (P>0.05). Also, in positive culture patients, the organisms recognized before and after surgery did not differ meaningfully (P>0.05) (Tables 1 & 2).

Table 1 Comparison of demographic characteristics and results of conjunctival microbial culture in two groups

Variable		Group		P-value*
		Case	Control	
Age (year), Mean ±SD		1.41±1.48	1.88±1.91	0.7451
Gender, n (%)	Male	39 (40.63%)	43 (44.79%)	0.6622
	Female	57 (59.37%)	53 (55.21%)	
Cultivating bacteria, n (%)	Positive	71 (73.96%)	35 (36.46%)	<0.00013
	Negative	25 (26.04%)	61 (63.54%)	
The number of types of bacteria in the sample, n (%)	Monomicrobial	63 (88.73%)	96 (100%)	0.0943
	Polymicrobial	8 (11.27%)	0 (0%)	
Type of bacteria, n (%)	Gram-positive	62 (75.61%)	29 (82.86%)	0.1813
	Gram-negative	20 (24.39%)	6 (17.14%)	
Number of colonies, Mean ±SD (In a sample unit), Mean ±SD	Before the operation	2849.91±2953.23	10.25±1.82	<0.00011
	First week	2647.29±2167.74	-	-
	Second week	1648.54±1218.27	-	-
	Third week	459.72±534.42	-	-
	Fourth week	10.78±4.38	-	-
The time it takes for the culture to return to normal, Mean ±SD		1.92±0.54	-	-
* P-value < 0.05 is considered significant. 1. Independent t-test 2. Fisher's exact test 3. Chi-square test				

Table 2 The bacteria type in positive cultures

Type of bacteria	Group		Organism
	Case	Control	
Gram-positive, n (%)	39 (54.93%)	18 (51.43%)	*Staphylococcus epidermidis*
	12 (16.90%)	6 (21.43%)	*Staphylococcus aureus*
	2 (2.82%)	-	*Staphylococcus Saprophyticus*
	6 (8.45%)	4 (14.29%)	*Streptococcus spp.*
	3 (4.23%)	1 (3.57%)	*Streptococcus pneumoniae*
Gram-negative, n (%)	7 (9.46%)	4 (14.29%)	*H. influenza*
	6 (8.45%)	1 (3.57%)	*Klebsiella ozaenae*
	3 (4.23%)	1 (3.57%)	*Bacillus*
	2 (2.82%)	-	*Escherichia coli*
	2 (2.82%)	-	*Diphtheroids*

The average number of conjunctival bacterial colonies in the control group was 10.25 ± 1.82 (between 0 and 60 colonies), and in the case group, it was 2849.91 ± 2953.23 colonies in each sample (P<0.0001). The repeated measures ANOVA analysis showed a significant difference between the evaluation stages of colony number (P<0.0001). No significant difference existed between the number of colonies before surgery and the first week after surgery (P=0.098). But at other times, a substantial decrease in the colony number was observed (P<0.0001).

The results showed no significant difference between the conjunctival bacteriology pattern (type of bacteria and number of colonies) with the age and gender of the patients (P=0.281 and P=0.778, respectively). The duration of conjunctival bacterial culture becoming negative or normal after successful probing surgery was 1.92 ± 0.54 weeks (between 1 and 3 weeks) (Figure 1). In the

fourth week, all subjects had normal conjunctival bacterial colony count. The average time to normalization of bacterial culture was not significantly related to age (r=0.123, P=0.305) and patients' gender (P=0.284), but it was related directly to the number of initial bacterial colonies ≥1000 and the silicone tube presence (P<0.0001) (Table 3).

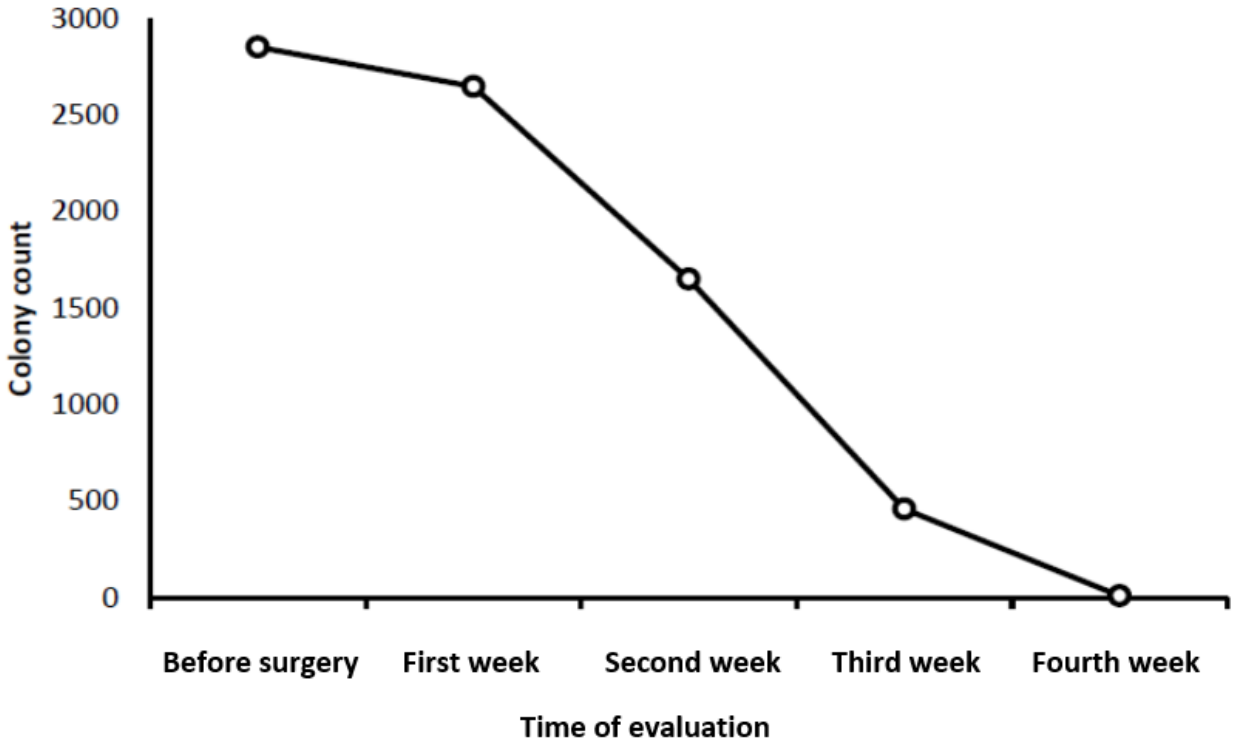

Figure 1 Changes in the number of bacterial colonies in the conjunctiva in children with NLDO before and after successful probing surgery

Table 3 Correlation between normalization duration of conjunctival bacterial culture with qualitative variables

Variable		Result	P-value*
Gender, mean ±SD	Female	2.03±0.60	0.2841
	Male	1.81±0.49	
Initial colony count	Colony counts <1000	1.32±0.31	0.0001
	Colony counts ≥1000	2.53±0.55	
Silicone tube	With	2.39±0.34	0.0001
	Without	1.44±0.70	
* P-value < 0.05 is considered significant. 1. Independent t-test			

4. DISCUSSION

Investigating the time, it takes for the culture of nasolacrimal duct secretions to become negative or similar to that of regular people in society is essential in patients who will undergo a second surgery like congenital glaucoma or cataract surgery to reduce complications such as endophthalmitis. In the present study, results showed a positive conjunctival bacterial culture in 71 (73.96%) of 5-1-year-old children with unilateral NLDO and 35 (36.46%) of the control group. Considering that the microbial flora of the two groups of children did not differ significantly and the bacteria detected before and after the operation were similar, it can be mention that the microorganisms usually present in the normal physiological flora of the conjunctiva due to CNLDO can become a pathogens agent. Many studies have reported positive conjunctival bacterial culture in 62.7 to 87.9% of children with NLDO (Usha et al., 2006; Yang et al., 2022).

This prevalence includes a high percentage in the adult population similar to children so, 71.9% in Kebede et al., (2010) study and 60.8% in Assefa et al., (2015) study reported. A positive culture with a low percentage also reported. In Natarajan et al., (2022)

study, positive culture with CNLDO reported in 27% of children, and the reason for the low rate of positive culture was the history of antibiotic use. Also, in the study of Bekmez et al., (2019), and his colleagues a positive conjunctival bacterial culture observed in 26.8% of children aged 1 to 3 years with CNLDO. Background reasons include ethnic and environmental differences, geographical location, climate changes, and habits. Local food can affect the distribution of conjunctival flora and are the reason for the difference in the results of the studies.

Time is also a significant factor in the impact of the conjunctival bacterial culture test. Yang et al., (2022) study the results showed the effects of positive conjunctival bacterial culture reported 45.8% to 100% between 2013 and 2020. In the present study, most bacterial species identified in both case and control groups were gram- positive (75.61% and 82.86%, respectively). The most common gram-positive species identified were *Staphylococcus epidermidis* and *Staphylococcus aureus*, and the most common gram-negative species were *H. influenza* and *Klebsiella*. Previous studies also showed that most conjunctival microbial cultures (46-90%) were gram-positive bacterial species, while gram-negative species included between 2.5 and 40% of pathogens (Zheng et al., 2020; Assefa et al., 2015). Xu and Zhang, (2022) study reported that the conjunctiva bacterial flora included 91.62% Gram-positive bacteria and 8.35% Gram-negative bacteria, and the most common species are *Staphylococcus epidermidis* and *Staphylococcus aureus*.

These results are in line with the findings of the present study. Similar to the study by Xu and Zhang, (2022) and the present study, the study of Gerkowicz et al., (2005) in Poland, 75% of children with lacrimal duct obstruction had a positive conjunctival bacterial culture, the most common bacterial species were *Staphylococcus epidermidis* (28%), and *Staphylococcus aureus* (22%). Gram-negative bacteria were also rare and observed in only 5% of cases. According to the existing reports, the conjunctival normal flora sac is also Gram-positive, especially *Staphylococcus* species and then *Streptococcus spp* (Ramesh et al., 2010; Zheng et al., 2020). According to the evidence and findings of the present study, the most common conjunctival flora bacteria are Gram-positive bacteria, especially *Staphylococcus* species, which should be considered for treatment and before intraocular surgery.

In studies, a high percentage of gram-negative bacteria culture also reported. In the study of Usha et al., (2006) and his colleagues, the microbial flora of the conjunctiva included 57% gram-positive and 43% gram-negative, and the most common gram-positive and gram-negative species were *S. pneumonia* and *H. influenza*. Unlike the present study and most similar studies, the percentage of Gram-negative bacteria was high in this study. The main reason for these differences may be the widespread use of antibiotics, which leads to changes in the conjunctival bacterial flora. In the present study, polymicrobial observed in 11.27% of children. In various other studies, polymicrobial was reported between 7.7 and 31.3% (Usha et al., 2006; Yang et al., 2022). Differences in geographic, environmental, racial, and history of antibiotic use can cause some differences in the results.

The results of this study showed that the average duration of conjunctival bacterial cultures becoming negative or normal was 1.92 ± 0.54 weeks (between 1 and 3 weeks). Before planning intraocular surgery, due to the risk of endophthalmitis, one should wait about 3-4 weeks to normalize the conjunctiva after the probing operation. In the study of Balikoglu-Yilmaz et al., (2016) and his colleagues, the normalization duration of conjunctival bacterial flora after dacryocystorhinostomy (DCR) in adults reported as 1.47 ± 1.08 weeks (between 1 and 5 weeks). In study Owji and Khalili, (2009), the normalization duration of conjunctival bacterial culture in adults after DCR operation reported to be 4.5 weeks on average (between 3 and 8 weeks). The difference in the normalization time of the conjunctival flora can be due to the different individual and environmental characteristics of the studies.

In the present study, the average time to normalization of the bacterial culture was not significantly related to the age and gender of the patients, still it had a direct and significant relationship with the number of initial bacterial colonies ≥ 1000 and the silicone tubes presence. In previous studies, the abundance of conjunctival bacterial species did not differ based on gender (Usha et al., 2006; Luo et al., 2021). In addition, in other studies, the normalization duration of the bacterial flora of the conjunctiva had a significant relationship with a higher initial colony count and the silicone tube presence (Eshraghi et al., 2016; Owji and Khalili, 2009). These results, consistent with the findings of the present study, show that it takes a few weeks after a successful lacrimal probing procedure to normalize the microbial flora of the conjunctiva, and this time depends on various factors, including the number of initial colonies and silicone tube presence.

However, this study faced some limitations, such as locational limitations (mono-center) for conducting the study, which can make the study results biased geographically and racially. The incubation of microorganisms depends on various conditions such as temperature, amount of carbon dioxide, and incubation time. Therefore, it is possible that some microorganisms in the lacrimal duct not identified in the studied conditions. Finally, more precise results can be attained by conducting more studies with a larger sample size, in a multi-center in different regions.

5. CONCLUSION

This study showed that most of children aged 1-5 years with NLDO who underwent successful lacrimal propping had positive bacterial cultures. Most cases were gram-positive and multi-microbial infections observed in 11.27% of patients. The results also showed no substantial change between the diversity of the microbial flora of the two groups. Therefore, the microorganisms that make up the normal physiological flora of the conjunctiva may become pathogenic agents due to lacrimal duct obstruction. In both groups, the most common gram-positive species identified were *Staphylococcus epidermidis* and *Staphylococcus aureus*, and the most common gram-negative species were *H. influenza* and *Klebsiella*. These results can help to decide the management and antibiotic treatment of this group of children in the study area.

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Ethical approval

The ethical code of the study in ethics committee is: IR.AJUMS.REC.1397.965

Informed consent

Written & Oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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