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Research

Culture-proven Bacterial Conjunctivitis in Newborns: Five-year Single-center Experience

Kültür Kanıtlı Yenidoğan Bakteriyel Konjonktiviteleri: 5 Yıllık Tek Merkez Deneyimi

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ABSTRACT

Objective: The data on neonatal conjunctivitis are significantly limited in Türkiye. In this study, we aimed to investigate the epidemiology of neonatal bacterial conjunctivitis and the clinical and laboratory findings of patients in a tertiary neonatal referral hospital in İstanbul, Türkiye.

Methods: This retrospective observational study was conducted over a five-year period between January 2015 and January 2020. Newborns 28 days of age who presented to our clinics with clinical features of conjunctivitis and had bacterial growth in the conjunctival culture were included.

Results: Thirty-two newborns with culture-proven bacterial conjunctivitis were included. A total of 26 (81.3%) newborns required newborn intensive care unit (NICU) admission. Gram-positive bacteria growth was detected in 47% (n=15) of cases, and gram-negative growth was detected in 53% (n=17) of cases. *Escherichia coli* (n=12), *Staphylococcus epidermidis* (n=10) and *Staphylococcus aureus* (n=3) were the most frequently identified bacteria. The proportions of newborns with need for intravenous (IV) antibiotic treatment, bilateral eye involvement, and normal spontaneous delivery were significantly higher in the gram-negative conjunctivitis group.

Conclusion: Our study provides important data regarding bacterial conjunctivitis in newborns in Türkiye, given that data in Türkiye are very limited. The high rates of NICUs admission, presence of clinical sepsis, and IV antibiotic administration show the importance of neonatal conjunctivitis as a clinical finding of systemic neonatal infections. Despite the lack of universal ocular prophylaxis in our high-volume neonatal referral center, the low number of culture-proven conjunctivitis cases challenges the current routine ocular prophylaxis suggestions.

Keywords: Conjunctivitis, ophthalmia neonatorum, newborn

ÖZ

Amaç: Türkiye'de yenidoğan konjonktiviti ile ilgili veriler oldukça sınırlıdır. Bu çalışmada İstanbul'da üçüncü basamak bir yenidoğan refereans merkezindeki neonatal bakteriyel konjonktivit epidemiyolojisini ve hastaların klinik ve laboratuvar bulgularını araştırmayı amaçladık.

Gereç ve Yöntem: Bu retrospektif gözlemsel çalışma, Ocak 2015 ile Ocak 2020 arasındaki beş yıllık dönemde gerçekleştirildi. Kliniğimize konjonktivit semptomları ile başvuran ve konjonktival kültüründe bakteri üremesi olan, 28 günlükten küçük yenidoğanlar çalışmaya dahil edildi.

Bulgular: Kültürle kanıtlanmış bakteriyel konjonktiviti olan 32 yenidoğan çalışmaya dahil edildi ve 26'sının (%81,3) yenidoğan yoğun bakım ünitesinde (YYBÜ) takibi yapıldı. Olguların %47'sinde (n=15) gram-pozitif bakteri üremesi, olguların %53'ünde (n=17) gram-negatif üreme saptandı. *Escherichia coli* (n=12), *Staphylococcus epidermidis* (n=10) ve *Staphylococcus aureus* (n=3) en sık tespit edilen bakterilerdi.

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ÖZ

Gram-negatif konjonktivit grubunda intravenöz (İV) antibiyotik tedavisi gerektiren, iki taraflı göz tutulumu olan ve normal spontan doğum ile doğan yenidoğan oranları anlamlı olarak daha yüksekti.

Sonuç: Çalışmamız verilerin oldukça sınırlı olduğu ülkemizde yenidoğanlarda bakteriyel konjonktivit ile ilgili önemli bulgular sunmaktadır. YYBÜ takibi ve İV antibiyotik gerektiren ve sepsis klinik bulguları olan yenidoğanların oranlarının yüksek olması, sistemik yenidoğan enfeksiyonlarının klinik bulgusu olarak yenidoğan konjonktivitinin önemini göstermektedir. Rutin oküler profilaksi uygulanmayan referans merkezimizdeki 5 yıllık süre zarfında kültürle kanıtlanmış konjonktivit olgularının az sayıda olması, mevcut rutin oküler profilaksi önerilerinin tekrar değerlendirilmesi gerektiği konusunda fikir vermektedir.

Anahtar Kelimeler: Konjonktivit, oftalmia neonatorum, yenidoğan

INTRODUCTION

Conjunctivitis, which is seen in the first month of life, is called ophthalmia neonatorum (ON). The ON incidence ranges from 1.6% to 12% (1). The most important cause of neonatal blindness globally was neonatal conjunctivitis before the twentieth century (2). Keratitis, dacryocystitis, nasolacrimal duct obstruction, cellulitis, and glaucoma are the differential diagnoses of neonatal conjunctivitis; and it has serious complications such as corneal ulcers, eye perforation, blindness, systemic spread; sepsis, meningitis, and pneumonia if left untreated (3). Although the clinical features of neonatal conjunctivitis, such as conjunctival erythema, edema, and discharge, are similar to those of conjunctivitis in older individuals, it is a medical condition that should be diagnosed and treated urgently in newborns, considering the possible disease progression and systemic infections that may accompany it.

The silver nitrate 2% prophylaxis recommended by Dr. Crede in 1881 was a turning point in ON (4). The rate of *Neisseria gonorrhoeae* infection in ON cases decreased from 10% to 0.3% in the post-prophylaxis period (5). Better prophylaxis options were tried because of chemical conjunctivitis, the common side effects of silver nitrate; and different antibiotic ointments and diluted povidone-iodine solutions have been used in ON prophylaxis. Today, there is still no clear consensus on ON prophylaxis, and each country and society has different suggestions regarding the role and method of universal ocular prophylaxis (6).

Although bacterial agents cause most conjunctivitis cases in the neonatal period, viral and chemical conjunctivitis are also observed in the neonatal period. Classically, the causative agents of bacterial conjunctivitis are *Chlamydia trachomatis* and *N. gonorrhoeae*, whereas gram-positive bacteria such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and viridans *Streptococci*; and gram-negative bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa*, and other gram-negative enteric bacteria are known to cause bacterial conjunctivitis (7).

The data on neonatal conjunctivitis are significantly limited in Türkiye. In this study, we aimed to investigate the epidemiology of neonatal bacterial conjunctivitis and the clinical and laboratory findings of patients in a tertiary neonatal referral hospital in İstanbul, Türkiye.

METHODS

Ethics

Our single-center study was retrospectively designed over a 5-year period between January 2015 and January 2020. Study approval was obtained from the University of Health Sciences Türkiye, Zeynep Kamil Maternity and Children's Training and Research Hospital Clinical Research Ethics Committee (decision no: 16, date: 20.01.2021). Consent was waived because of the retrospective nature of the study.

Study Population and Inclusion Criteria

Demographic and clinical characteristics, such as birth weight, gestational age, mode of delivery, postnatal age, maternal data, and laboratory data, were obtained from electronic medical records. Newborns 28 days of age who presented to our clinics with clinical features of conjunctivitis and had bacterial growth in the conjunctival culture were included in our study. Only community-acquired conjunctivitis cases were included. Hospital-acquired conjunctivitis cases based on the Centers for Disease Control and Prevention guidelines were excluded (8).

Study Setting and Conjunctivitis Diagnosis

A total of 39,138 babies were delivered in our tertiary referral center over 5 years. An average of 1500 newborns were admitted to our neonatal intensive care unit (NICU) annually. Eyecare with normal saline and gauze is routinely performed for babies born in our hospital, but conjunctivitis prophylaxis is not administered. Newborns are discharged from the newborn nursery at least 24 h after normal spontaneous delivery (NSD) and 48 h after cesarean section. Conjunctival cultures were obtained from newborns with clinical findings of conjunctivitis in our hospital's outpatient clinics, nursery services, and NICUs. In preparation for culture, the

periorbital area was cleaned with sterile gauze and normal saline. Culture was taken from the lower conjunctiva using a cotton swab. Particular attention was paid to prevent touching eyelids and eyelashes while taking the culture. The sample taken on a cotton swab was transferred to a transport tube containing the medium. Culture inoculation, microbiological identification, and antibiotic susceptibility tests were performed in a microbiology laboratory. Management and follow-up were performed by attending pediatricians, neonatologists, or ophthalmologists. While topical antibiotic treatment was administered to all patients, intravenous (IV) antibiotic treatment and hospitalization were deemed necessary for some newborns when systemic infection was suspected.

Statistical Analysis

Statistical analysis was performed using Stata version 17.0 (Stata Corp LLC, College Station, Texas). The distribution of continuous variables was assessed using histograms and statistical methods. Continuous variables were presented as "mean ± standard deviation" or median [interquartile range (IQR) 25-75 percentile] according to the distribution normality; and categorical variables were presented as "number (percentage)". Patients were divided into two groups based on the bacteria causing conjunctivitis: gram-positive and gram-negative groups. Comparison of categorical variables between groups was made using the chi-square or Fisher's exact test. Comparison of continuous variables was performed using Student's t-test or Mann-Whitney U test if normality assumptions were not met. A $p<0.05$ level was set for statistical significance.

RESULTS

Thirty-two newborns with clinical signs of conjunctivitis and bacterial growth on conjunctival cultures were included in our study during the 5-year study period. While 43.8% (n=14) of the patients were female, 56.2% (n=18) were male. The mean birth weight and gestational age were 3024±728 grams and 37.6±2.8 weeks, respectively (Table 1).

Unilateral involvement was noted in 56.3% of the patients (n=18), and 43.7% (n=14) had bilateral conjunctivitis. Conjunctival edema (chemosis) was detected in 21.9% patients. A total of 26 (81.3%) newborns required NICU admission, and the indication for NICU admission was conjunctivitis in 6 patients. Other indications for NICU admission were respiratory distress (n=11), prematurity (n=5), jaundice (n=3) and congenital malformation (n=1). Neonatal sepsis was clinically diagnosed in 14 patients. Only two of them had culture-proven sepsis, and both blood and conjunctival cultures grew the same bacteria. IV antibiotic treatment was initiated in 62.5% (n=7) of the patients for a median of 7 (IQR 6-10) days. High C-reactive protein (>1 mg/dL) was found in 18.7% (n=6) of the patients. The clinical and laboratory data of our cohort are shown in Table 2.

In conjunctival cultures, gram-positive bacteria growth was detected in 47% (n=15) of cases, and gram-negative growth was detected in 53% (n=17) of cases. *E. coli* (n=12), *S. epidermidis* (n=10) and *S. aureus* (n=3) were the most frequently identified bacteria in the study. The etiological distribution of the 32 neonatal conjunctivitis cases in our study is reported in Table 3.

The majority of neonatal conjunctivitis cases were diagnosed in spring (43.8%), followed by summer (37.5%), fall (6.2%), and winter (12.5%) months. There was a statistically significant seasonal difference between gram-positive and gram-negative conjunctivitis cases. All gram-negative conjunctivitis cases were diagnosed in spring and summer months, whereas 60% (n= 9) of gram-positive conjunctivitis

Table 1. Demographic features of newborns with culture-proven conjunctivitis

Demographic features	n=32
Gender, girl*	14 (43.8)
Birth weight, gram[1]	3024±782
Gestational age, week[1]	37.6±2.8
Mode of delivery, NSD*	18 (56.3)
Maternal age, year[1]	29.3±6.3
Oligohydramnios*	3 (9.4)
Premature rupture of membrane*	2 (6.3)

*n (%), [1]Mean ± standard deviation, NSD: Normal spontaneous delivery

Table 2. Clinical and laboratory findings of newborns with culture-proven conjunctivitis

Clinical findings	n=32
Unilateral eye involvement*	18 (56.3)
Conjunctival edema*	7 (21.9)
Clinical sepsis*	14 (43.8)
Culture-proven sepsis*	2 (6.3)
NICU admission*	26 (81.3)
Length of stay in NICU[2]	9 (2-60)
Intravenous antibiotic use*	20 (62.5)
Length of intravenous antibiotic use, day[2]	7 (6-10)
Laboratory findings	
Leucocyte x1000/μL[1]	14.7±5.7
Neutrophil x1000/μL[1]	8.5±4.7
Thrombocyte x1000/μL[1]	287±128
C-reactive protein, mg/dL[2]	0.2 (0.1-0.54)

*n (%), [1]Mean ± standard deviation, [2]Median (IQR), NICU: Newborn intensive care unit, IQR: Interquartile range

cases were detected in spring and summer months (p=0.01). The seasonal distribution of conjunctivitis cases is shown in Table 4.

Of the 32 neonatal conjunctivitis cases in our study, 25 (78.2%) were diagnosed in the first week of life, followed by 4 (12.5%) in the second week of life, 2 (6.2%) in the third week of life, and 1 (3%) in the fourth week of life. Gram-negative conjunctivitis cases were diagnosed earlier than gram-positive cases [1 (IQR 1-3) days vs. 6 (IQR 3-11) days, p=0.002] and all gram-negative conjunctivitis cases were diagnosed in the first week of life (Figure 1).

Newborns with gram-negative conjunctivitis had a significantly higher proportion of NSD delivery (76.5%) than those with gram-positive conjunctivitis (33.3%, p=0.01) Bilateral eye involvement was present in 26.7% (n= 4) of newborns with gram-positive conjunctivitis and 58.8% of newborns with gram-negative conjunctivitis. This difference between the groups was statistically significant (p=0.04). The need for IV antibiotics was higher in the gram-negative conjunctivitis group (p=0.01). Complete demographics and clinical characteristics comparison between the gram-negative and gram-positive groups are shown in Table 5.

Table 3. Etiology of culture-proven neonatal conjunctivitis

	n=32
Gram-positive*	**15 (47)**
*Staphylococcus epidermidis**	10 (31.2)
*Staphylococcus aureus**	3 (9.4)
*Streptococcus pneumoniae**	1 (3.1)
Corynebacterium spp.*	1 (3.1)
Gram-negative*	**17 (53)**
*Escherichia coli**	12 (37.5)
*Klebsiella pneumoniae**	2 (6.3)
*Enterobacter aerogenes**	1 (3.1)
*Pseudomonas aeruginosa**	1 (3.1)
*Neisseria gonorrhoeae**	1 (3.1)

*n (%)

Table 4. Seasonal distribution of conjunctivitis

Season	Overall n=32	Gram-positive n=15	Gram-negative n=17	p-value
Spring*	14 (43.8)	6 (40)	8 (47.1)	0.01
Summer*	12 (37.5)	3 (20)	9 (52.9)	
Fall*	2 (6.2)	2 (13.3)	0 (0)	
Winter*	4 (12.5)	4 (26.7)	0 (0)	

*n (%)

DISCUSSION

Although complications due to neonatal conjunctivitis have decreased considerably worldwide, it remains a significant cause of neonatal morbidity. Unfortunately, our data do not provide a reliable incidence rate because some patients might have been treated empirically without obtaining conjunctival culture. However, the fact that the total number of culture-proven conjunctivitis cases in 5 years was only 32 is an important clue regarding its incidence considering the significantly high volume of patients who have been delivered and seen in our referral center. In the setting of a low number of cases, we speculate that our approach of no eye chemoprophylaxis after delivery did not result in high numbers of neonatal conjunctivitis cases, although this remains to be proven in large prospective studies.

Classical neonatal conjunctivitis pathogens, *C. trachomatis* and *N. gonorrhea*, are sexually transmitted diseases (STD) and newborns acquire these bacteria during the perinatal period; and the lack of robust STD incidence in childbearing aged women is an important obstacle to understanding the burden of neonatal conjunctivitis and the need for universal prophylaxis in our country. The current recommendation by the Turkish Ministry of Health is universal conjunctivitis prophylaxis according to "Basic Newborn Care" book published by the General Directorate of Public Health (9). However, each clinic makes its own instructional decision. In a study including 48 hospitals in Türkiye, 42% of the hospitals did not routinely administer conjunctivitis prophylaxis; and there was no consensus regarding prophylaxis methods among hospitals applying routine prophylaxis (10). Seven different agents were administered in prophylaxis-applying hospitals (10). The debate over the utility of conjunctivitis prophylaxis is not unique to Türkiye. A study conducted by the American Pediatric Ophthalmology and Strabismus Society surveyed 291 members working in different countries and continents and found that conjunctivitis prophylaxis was not performed in 21% of survey participating hospitals (11).

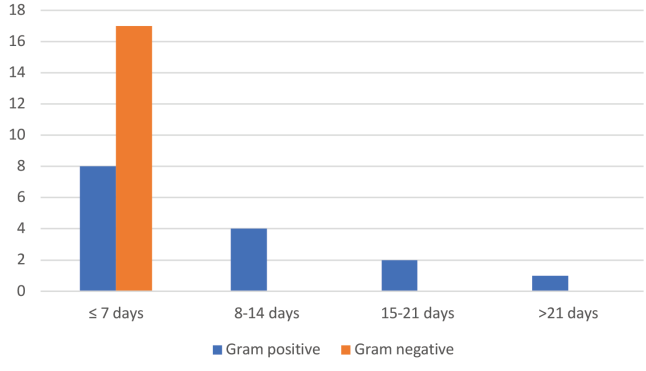

Figure 1. Postnatal age at the conjunctivitis diagnosis

Table 5. Comparison of patient data between gram-positive and gram-negative groups

	Gram-positive n=15	Gram-negative n=17	p-value
Gender, girl*	6 (40)	8 (47.1)	0.6
Birth weight, gram[1]	3095±841	3000±739	0.7
Gestational age, week[1]	37±2.7	38.2±2.6	0.1
Mode of delivery, NSD*	5 (33.3)	13 (76.5)	0.01
Maternal age, year[1]	31±6.6	27.5±5.7	0.1
Oligohydramnios*	0 (0)	3 (17.6)	0.2
Premature rupture of membrane*	0 (0)	2 (11.8)	0.4
Unilateral eye involvement*	11 (73.3)	7 (41.2)	0.04
Conjunctival edema*	3 (20)	4 (23.5)	1
Clinical sepsis*	5 (33.3)	9 (52.9)	0.2
Culture-proven sepsis*	1 (6.7)	1 (5.9)	1
NICU admission*	11 (73.3)	15 (88.2)	0.3
Length of stay in NICU[2]	7 (2-54)	9 (4-60)	0.9
IV antibiotic use*	6 (40)	14 (82.4)	0.01
Length of IV antibiotic use, day[2]	8 (7-10)	7 (6-10)	0.6
Leucocyte x1000/µL[1]	15.4±5.7	14.3±5.9	0.6
Neutrophil x1000/µL[1]	7±3.2	9.4±5.3	0.2
Thrombocyte x1000/µL[1]	334±149	257±107	0.1
C-reactive protein, mg/dL[2]	0.2 (0.2-0.4)	0.2 (0.2-1.2)	0.9

*n (%), [1]Mean ± standard deviation, [2]median (IQR), NSD: Normal spontaneous delivery, NICU: Newborn intensive care unit, IV: Intravenous, IQR: Interquartile range

Although the estimated rate of neonatal conjunctivitis due to *N. gonorrhea* in the United States is less than 1 case per 100,000 livebirth, the United States Preventative Service Task Force still recommends universal prophylaxis because of high perinatal transmission rates without ocular prophylaxis and significant morbidity related to gonococcal conjunctivitis (12).

The absence of erythromycin's prophylactic effect against *C. trachomatis* infections (13) and lack of literature support for universal ocular prophylaxis have raised questions about the necessity of universal ocular prophylaxis (14). Selecting antibiotic-resistant pathogens is another concern regarding routine antibiotic prophylaxis, and some experts suggest using a 2.5% povidone-iodine solution rather than antibiotic ointments for prophylaxis because of the increasing antibiotic resistance in neonatal conjunctivitis (15). Implementing strong maternal STD screening and treatment programs would further decrease the need for universal prophylaxis in our country and globally (16).

Although most of the clinical and laboratory findings were similar between gram-negative and gram-positive conjunctivitis cases, there were also remarkable differences. Newborns with gram-negative conjunctivitis were diagnosed earlier and had a more severe disease course (bilateral eye involvement, need for IV antibiotics) than gram-positive cases. The higher proportion of NSD in the gram-negative group than in the gram-positive group likely reflects the acquisition of causative pathogens from maternal genitourinary flora during passage through the birth canal (17). Similar to previous studies, our study detected conjunctivitis cases most commonly in the spring and summer (18). This seasonal difference was more prominent in gram-negative conjunctivitis cases in this study.

S. epidermidis was one of the most common etiologies of bacterial neonatal conjunctivitis in our study. The importance of coagulase-negative *Staphylococci* growth in conjunctival culture is controversial. Historically, coagulase-negative *Staphylococci* have been accepted as contaminants in conjunctival cultures (19). However, more recent studies have considered *S. epidermidis* as a causative agent in conjunctivitis. In one systematic review, *S. epidermidis* was found to be the second most common bacterial ocular infection pathogen after *S. aureus* (19). There is also emerging evidence that *S. epidermidis* can cause inflammation and infection in the conjunctiva and eyes (19).

Although we had a low number of newborns with culture-proven bacterial conjunctivitis, the percentage of patients who needed conjunctivitis-related NICU admission and IV antibiotics was relatively high. Moreover, two patients had culture-proven sepsis with the same bacteria found in the conjunctival culture, and 43% of the newborns with

conjunctivitis had clinical sepsis. Our findings suggest that prompt diagnosis and treatment of neonatal conjunctivitis is crucial, and conjunctivitis can be an initial symptom of more severe systemic infection. Contrary to our results, only 3/52 patients (6%) received IV antibiotics in a recent study from Canada; however, only 5 patients had culture-proven neonatal conjunctivitis in their study (20).

The retrospective design and small cohort were the most important limitations of our study. Another important limitation was the lack of access to molecular diagnostic tests for *C. trachomatis*. Although the incidence of *C. trachomatis* positivity in women is low in Türkiye (19), it is still one of the most common causes of newborn conjunctivitis.

CONCLUSION

In conclusion, our study provides important data regarding bacterial conjunctivitis in newborns in Türkiye, given that data in Türkiye are very limited. The high rates of NICU admission, presence of clinical sepsis, and IV antibiotic administration show the importance of neonatal conjunctivitis as a clinical finding of systemic neonatal infections. Despite the lack of universal ocular prophylaxis in our high-volume neonatal referral center, the low number of culture-proven conjunctivitis cases challenges the current routine ocular prophylaxis suggestions. Only one patient had gonococcal conjunctivitis, which is a historical target of ocular prophylaxis. However, our results may not be generalizable because of their single-center nature. Prospective multicenter studies in Türkiye are needed to better answer the question of ocular chemoprophylaxis.

ETHICS

Ethics Committee Approval: Study approval was obtained from the University of Health Sciences Türkiye, Zeynep Kamil Maternity and Children's Training and Research Hospital Clinical Research Ethics Committee (decision no: 16, date: 20.01.2021).

Informed Consent: Consent was waived because of the retrospective nature of the study.

Authorship Contributions

Surgical and Medical Practices: S.D., H.A., G.Ç., S.T., G.K., Concept: S.D., H.A., Design: S.D., H.A., Data Collection or Processing: S.D., H.A., G.Ç., S.T., F.E., Analysis or Interpretation: S.D., Literature Search: S.D., Writing: S.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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