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RESEARCH ARTICLES

Evaluation of the effectiveness of pentoxifylline use in neonatal sepsis

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ABSTRACT

Aim: Neonatal sepsis is an infection of the bloodstream in infants under 28 days old. It remains a leading cause of morbidity and mortality among infants. For this reason, it is important to closely monitor patients and initiate early and effective treatment when sepsis is suspected. In some cases, supportive treatments are needed in addition to appropriate antibiotic therapy to ensure clinical stability. This study aims to evaluate the effectiveness of pentoxifylline (PTX) use as a supportive treatment for neonatal sepsis.

Materials and Methods: Patients who were followed up in our clinic with a diagnosis of sepsis between January 2020 and December 2024 and who had pentoxifylline added to their treatment were included in the study. Patient data were obtained from patient files, the hospital patient record, and the follow-up system, and evaluated retrospectively.

Results: All patients who were followed up for sepsis and treated with pentoxifylline were evaluated. A total of 45 infants were included in the study. Nine patients died due to sepsis in the early period. Therefore, early morbidity outcomes were evaluated based on the remaining 36 patients. Another patient died on the 67th day of life, bringing the total mortality count to 10. Demographic, clinical and laboratory data of the patients were shown in tables. It was observed that the frequency of mortality, bronchopulmonary dysplasia, and necrotizing enterocolitis (NEC) in our patients was higher than the reported national/international averages.

Conclusion: In our study, the mortality and short-term morbidity rates, including necrotizing enterocolitis and bronchopulmonary dysplasia, were found to be higher than those reported in the literature. This may be due to pentoxifylline being administered to patients with impaired circulation and added late to the treatment. Randomized controlled studies with larger patient samples and more homogeneous clinical conditions are needed to more accurately reveal the effect of pentoxifylline on neonatal mortality and morbidity.

Keywords: NICU, pentoxifylline, sepsis, supportive treatment

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INTRODUCTION

Neonatal sepsis is an infection of the bloodstream in infants younger than 28 days old (1,2). Despite advances in neonatology, sepsis remains an important cause of infant mortality and morbidity (3). Therefore, close monitoring of infants and the prompt initiation of effective treatment are crucial when sepsis is suspected.

According to the timing and route of infection, neonatal sepsis is classified into two main categories. Early-onset sepsis (EOS) typically caused by vertical transmission of invasive pathogens from the mother during labor or delivery. It is diagnosed when microbiological cultures are positive within the first seven days of life. In contrast, late-onset sepsis (LOS), also referred to as nosocomial sepsis, occurs after the first week of life and is usually attributed to the postnatal acquisition of pathogens, either from hospital (nosocomial) or community sources. Empirical antibiotic therapy should be selected according to these classifications, while also considering the local microbial flora and resistance patterns specific to the clinical setting (4).

In some cases, supportive treatments are needed in addition to appropriate antibiotic therapy to ensure clinical stability (5). Therapies such as granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, and immunoglobulin do not significantly improve outcomes in preterm neonates with sepsis (6,7). Pentoxifylline (PTX), a derivative of methylxanthine, works as a phosphodiesterase inhibitor and shows anti-hemorrhagic, anti-proliferative, and immunomodulatory effects. As a result, it leads to improved microcirculation and tissue perfusion. Pentoxifylline also has an anti-inflammatory effect against Toll-like receptor –mediated production of cytokines (8,9).

This study aims to evaluate the effectiveness of pentoxifylline using as a supportive treatment for neonatal sepsis.

MATERIALS AND METHODS

This study was designed as a single-center, retrospective analysis carried out in the NICU of our tertiary-level hospital. The study included patients who were hospitalized and treated in the NICU between January 2020 and December 2024 and were diagnosed with proven, clinical, or suspected sepsis. The EMA Sepsis Scoring System was employed to support early recognition and management, in accordance with the Turkish Neonatology Society's Guideline on the Diagnosis and Treatment of Neonatal Infections (10). Clinical criteria included temperature instability and respiratory findings such as apnea, tachypnea, and an increased need for respiratory support; cardiovascular signs such as bradycardia, tachycardia, and hypotension; and signs of impaired peripheral perfusion. Laboratory findings that were considered supportive of sepsis included leukopenia or leukocytosis (white blood cell count >20,000/mm^3), an elevated immature-to-total neutrophil ratio (≥0.2), thrombocytopenia (<100,000/mm^3), CRP >15 mg/L (1.5 mg/dL), procalcitonin >2 ng/mL, hypoglycemia or hyperglycemia (<45 or >180 mg/dL), and metabolic acidosis on blood gas analysis (base excess >–10 mEq/L or serum lactate >2 mmol/L).

Infants with congenital heart disease, syndromic features, or known neurometabolic disorders were excluded from the study.

PTX was added to the treatment for cases of sepsis with impaired tissue perfusion. PTX was used at a dosage of 6 mg/kg/h infused over 6-h daily for six days. All demographic, clinical, and laboratory data of the participants were obtained retrospectively from their medical records. Patient data were accessed from patient files and the Enlil Hospital Information System database, which is the hospital's patient registration and tracking system.

Demographic and clinical data of the patients, including gender, gestational age, birth weight, mode of delivery, and maternal age, were recorded.

Laboratory parameters, blood culture results, sepsis classification, pentoxifylline treatment status, and the timing of its initiation were also documented. Sepsis was classified based on the time of onset (early vs. late-onset). Laboratory evaluations included C-reactive protein (CRP) levels and hematological indices such as white blood cell (WBC) and platelet (PLT) counts, as well as the presence or absence of microbial growth in blood cultures. Clinical outcomes assessed during the follow-up period included mortality and short-term morbidities, particularly necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), and retinopathy of prematurity (ROP).

The statistical analysis was performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the data. Continuous variables were presented as the mean ± standard deviation for normally distributed data or as the median (minimum–maximum) for skewed distributions. Categorical variables were expressed as numbers and percentages. Since this was a descriptive study without group comparisons, no inferential statistical tests were applied.

RESULTS

Patients diagnosed with sepsis and treated with pentoxifylline were included in the analysis. A total of 45 infants were included in the study. Nine patients died due to sepsis in the early stage. Therefore, early morbidity outcomes were evaluated based on the remaining 36 patients. Another patient died on the 67th day of life, bringing the total mortality count to 10.

Table 1 shows the demographic features. As expected, the majority of the infants were born prematurely and had low birth weights. The majority of the infants were appropriate for gestational age and were delivered via cesarean section. The number of male and female infants was approximately equal.

Sepsis-related laboratory parameters are summarized in Table 2. PTX treatment was administered to 45 patients due to nosocomial sepsis (80%). In 64% of our patients, pathogens were isolated by culture antibiogram, and most of them were gram (-) bacteria.

Table 1. Demographic characteristics of the patients

Characteristic	PTX group (N=45)
Gestational week (week)	28.8 ± 5.2
mean ± SD (min-max)	(22 - 40)
Birth weight (gram)	1320 ± 858
mean ± SD (min-max)	(560 - 3950)
SGA	11 (24%)
AGA	27 (60%)
LGA	7 (16%)
Female	21 (47%)
Maternal Age	26.9
mean (min-max)	(18 - 39)
Cesarean Section delivery (C/S)	33 (73%)
Spontan vaginal delivery	12 (27%)

*SGA: Small for gestational age; AGA: Appropriate for gestational age; LGA: Large for gestational age.

The choice of antibiotic was made in collaboration with the pediatric infectious diseases department.

Data on mortality and short-term morbidities such as BPD, NEC, and ROP are summarized in Table 3. Ten patients died in the early period of the septic attack. For this reason, BPD and ROP evaluations were made on 35 patients. In our study, the mortality rate was found to be 46 percent.

DISCUSSION

The incidence of neonatal sepsis is generally reported as 1 to 5 cases per 1,000 live births, with higher frequencies observed in infants with lower gestational age and birth weight (11). Consistent with the literature, similar findings were observed in our study.

The primary method of preventing neonatal infections should be to protect the newborn against infections. The main subjects emphasized here are hand hygiene, umbilical cord care, eye prophylaxis, skin care, breastfeeding, protection against central vascular catheter-related infections and ventilator-associated pneumonia, avoidance of prolonged and broad-spectrum antibiotics, and protection against invasive Candida infections (12).

Table 2. Laboratory parameters of patients	
Parameter	**PTX group (n=45)**
Early-onset sepsis (+)	9 (20%)
Nosocomial sepsis	36 (80%)
Blood culture (+)	29 (64%)
WBC count at diagnosis (K/µL) Mean ± SD Median (min–max)	 18,670 ± 19,057 13,300 (1,050–85,800)
Platelet count at diagnosis (K/µL) Mean ± SD Median (min–max)	 173,200 ± 140,366 136,000 (10,000–654,000)
CRP at diagnosis (mg/L) Mean ± SD Median (min–max)	 61.8 ± 57 36 (17–159)
WBC count after pentoxifylline (K/µL) Mean ± SD Median (min–max)	 18,491 ± 12,371 16,200 (400–54,100)
Platelet count after pentoxifylline (K/µL) Mean ± SD Median (min–max)	 148,142 ± 155,166 84,000 (7,000–616,000)

Table 3. Short-Term Morbidity and Mortality Rates and Hospitalization stay	
Parameter	**PTX group (n=45)**
Bronchopulmonary dysplasia (BPD)	13 (37%)
Necrotizing enterocolitis (NEC) stage ≥2	11 (24%)
Retinopathy of prematurity (ROP), treatment-requiring	3 (8.5%)
Length of hospital stay (days)	
Mean ± SD	59.6 ± 65.9
Median (min–max)	35 (6–262)
Sepsis-related early mortality	10 (22%)
All-cause mortality	21 (46%)

BPD: Bronchopulmonary dysplasia; NEC: Necrotizing enterocolitis; ROP: Retinopathy of prematurity.

For infants showing signs and symptoms of infection, an empirical antibiotic treatment should be started as soon as culture samples are obtained, based on the time of onset, the environment in which the agent was acquired, and the focus of the infection, and according to possible agents and antibiotic sensitivity, and the treatment process should be planned in light of culture results, clinical follow-up, and repeated laboratory tests if necessary (13). The majority of the infants included in our study experienced clinical deterioration after the seventh day of hospitalization. The selection of empirical antibiotics for these infants, who were considered to have nosocomial sepsis, was guided by the recommendations of the Turkish Neonatal Society and tailored to the pathogens commonly isolated in our clinic (14).

In cases of sepsis, intensive supportive treatment should be started together with antibiotic therapy. Electrolyte and glucose levels should be kept within normal limits, appropriate fluid-electrolyte therapy should be applied, acidosis and hypovolemia should be prevented, shock should be recognized early, and inotropic drugs should be used in addition to fluid therapy when necessary. Nutritional support should also be maintained. Hypoxia should be corrected (10). We continued to apply the necessary supportive treatment modalities along with antibiotic therapy during our follow-ups. In addition to standard supportive strategies, pentoxifylline was administered to neonates with circulatory dysfunction due to its anti-inflammatory properties and beneficial effects

on microcirculation (15). Despite implementing of all supportive treatments, selecting appropriate antibiotic therapy, and using pentoxifylline as an adjuvant treatment, the mortality rate in our cohort (sepsis-related early mortality 22%, all-cause mortality 46%) was higher than the mortality rates reported in the literature for neonatal sepsis. In a meta-analysis conducted by Carolin et al., studies from 14 countries were evaluated, and the incidence of neonatal sepsis was reported as 2,824 per 100,000 live births and 17.6% died (16). This may be attributed to the fact that pentoxifylline was administered to patients with already impaired circulation and was introduced relatively late in the course of treatment in our study. BPD developed in 13 of our patients who could be evaluated for BPD (37 %), 11 of whom were premature. As expected, the incidence of bronchopulmonary dysplasia (BPD) was high among preterm infants (17). Our literature review revealed no studies evaluating the use of systemic pentoxifylline for the prevention of BPD. Further randomized controlled trials are needed in this field. Eleven (24%) of our patients developed stage 2 or higher NEC according to the Modified Bell Criteria. In our literature review, we found no studies specifically investigating the use and effects of pentoxifylline in neonates diagnosed with necrotizing enterocolitis. Similar to the mortality findings, we believe that the higher incidence of NEC compared to the rate reported in the Turkish Neonatal Society Necrotizing Enterocolitis Guideline may be related to the fact that pentoxifylline treatment being added at a later stage, after the development of circulatory compromise in the patients included in our study (18). Only three of our cases developed retinopathy of prematurity requiring intervention (laser photocoagulation). The gestational ages of these infants at birth were 23, 26, and 28 weeks, respectively. In the study conducted by Erbaş et al., the rate of Stage 3 or higher ROP in patients receiving high-dose pentoxifylline was reported as 10.3% (9). However, in our cohort, the incidence of treatment-requiring ROP was lower (8.5%). The lower incidence observed in our study may be explained by the fact that infants who died in the early postnatal period were excluded from ROP evaluation, and the analysis was therefore limited to 35 surviving neonates.

Limitations

An important limitation of this study is the absence of a control group consisting of patients who did not receive pentoxifylline. Since the study was conducted exclusively on neonates treated with pentoxifylline for sepsis, no internal comparison could be made between users and non-users. As a result, while the findings were interpreted in light of existing literature, direct conclusions about the efficacy of pentoxifylline in our clinical are limited. This limitation has been recognized as a methodological shortcoming and should be taken into account in future prospective, controlled studies.

CONCLUSION

In this study, we were unable to demonstrate a statistically significant benefit of adjuvant pentoxifylline therapy in treating neonatal sepsis. The lack of observed efficacy may be attributed to factors such as the severity of the illness in the study population and the delayed initiation of pentoxifylline treatment. These limitations underscore the importance of further research.

To accurately evaluate the therapeutic potential of pentoxifylline in neonatal sepsis, well-designed, randomized controlled trials should be conducted in larger and more homogeneous patient populations, using standardized protocols and clearly defined timing for drug administration.

Ethical approval

This study has been approved by the Selcuk University Rectorate Local Ethics Committee (approval date 11.02.2025, number 2025/66).

Author contribution

Surgical and Medical Practices: SSU; Concept: SSU; Design: SSU; Data Collection or Processing: SSU; Analysis or Interpretation: SSU; Literature Search: SSU; Writing: SSU. The author reviewed the results and approved the final version of the article.

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Conflict of interest

The author declare that there is no conflict of interest.

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