Pharmaceutical Sciences. 2026;32(1):160-166
doi:10.34172/PS.026.42133
https://ps.tbzmed.ac.ir/

Original Article

Pentoxifylline Effects on Late-Onset Sepsis in Preterm Neonates: A Pilot Randomized Clinical Trial

Sajad Khiali[1], MohammadBagher Hosseini[2], Manizheh Mostafa Gharehbaghi[3], Parvin Sarbakhsh[4], Donya Behzadi Mohammadi[5], Hila Asham[5], Elnaz Shaseb[5,6*]

[1]Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Pediatric Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Departments of Neonatology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[4]Road Traffic Injury Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[5]Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran
[6]Drugs Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

ARTICLE INFO

Article History:
Received: January 11, 2025
Revised: April 24, 2025
Accepted: July 19, 2025
ePublished: January 5, 2026

Keywords:
Clinical trial, Pentoxifylline, Sepsis, Late-onset sepsis, Preterm neonates

Abstract

Background: Despite the progress in the management of late-onset sepsis (LOS), it is the leading cause of mortality in preterm infants worldwide. Pentoxifylline is a methylxanthine with well-documented immunomodulatory properties, which may be an important approach to treating LOS.This study aimed to evaluate the efficacy and safety of adding oral pentoxifylline standard care among preterm neonates with LOS.

Methods: In this trial, 47 preterm neonates with a confirmed diagnosis of LOS were allocated to either receive Pentoxifylline 10 mg/kg three times a day orally plus standard care (n=23) or the standard care alone for 6 days (n=24) using the block randomization method. The primary outcomes were the duration of C-reactive protein (CRP) negativity, duration of supplemental oxygen therapy, hospitalization and mortality rate. Secondary outcomes included the assessment of any adverse events that may have occurred during the study. Continuous data were analyzed using the independent t-test or Mann–Whitney U test. Chi-square and/or Fisher's exact tests are used for categorical variables. The logistic regression analysis was also used for comparing mortality after adjusting for covariates.

Results: The demographic characteristics, mothers/infants-related risk factors, use of antenatal steroids, neonatal resuscitation, antibiotic regimen, and surfactant administration were statistically similar between the intervention and control groups; however, respiratory support significantly differed. After adjusting for respiratory support, there was no significant difference regarding the duration of hospitalization ($P=0.56$), CRP negativity ($P=0.69$), supplemental oxygen therapy ($P=0.94$), and mortality rate ($P=0.5$) between the study groups.

Conclusion: Adding oral pentoxifylline to standard care had no significant benefits on clinical and paraclinical outcomes in preterm neonates with LOS. Further clinical trials are needed to test the study hypothesis.

Introduction

Late-onset sepsis (LOS) is an infection that appears in a newborn after 72 hours of life. Microorganisms obtained in the community or during medical care in patients who require hospitalization induce LOS.[1] Although newborn baby mortality has improved significantly in recent years, their treatment requires procedures such as endotracheal intubation, catheters, lines, and broad-spectrum antibiotics, which increase their risk of nosocomial infection.[2] In the neonatal intensive care unit (NICU), LOS is a primary cause of death. In the first 120 days of life, the incidence of LOS in preterm newborns ranges from 20 to 38%, with death rates ranging from 13 to 19%.[3-5]

Pentoxifylline inhibits erythrocyte phosphodiesterase, boosting intracellular cyclic adenosine monophosphate activity and reducing inflammation. It also inhibits potent pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), Interleukin-6 (IL-6), and interferons.[6] It may also improve the antiaggregatory and vasodilatory actions of endogenous prostacyclin.[7] Furthermore, pentoxifylline increases erythrocyte flexibility, tissue plasminogen activator (tPA) activity, and fibrinolytic activity and decreases platelet adhesion. These could improve microcirculation, tissue perfusion, and blood viscosity.[8]

***Corresponding Author:** Elnaz Shaseb, Email: shasebe@tbzmed.ac.ir

Pentoxifylline, an immunomodulating agent, has recently been proposed to benefit preterm neonates with sepsis characterized by inflammatory cytokine cascade activation, free radical toxicity, and impaired microcirculation.[9] The potential benefits of pentoxifylline have been investigated in clinical trials. A double-blind, randomized controlled trial also indicated the beneficial effects of intravenous pentoxifylline 5 mg/kg/h for 6 hours on 6 successive days in preterm infants with LOS. However, there are uncertainties regarding the optimal dose, duration, and route of administration of pentoxifylline in preterm neonates with LOS.[10]

Given the above, we aimed to evaluate the effects of adding oral pentoxifylline 10 mg/kg three times a day for six days to standard care on the duration of hospitalization, C-reactive protein (CRP) negativity, and supplemental oxygen therapy, as well as the mortality rate in preterm infants with LOS.

Methods

Study design and setting

This study was a prospective randomized clinical trial conducted from May 4th, 2020, to September 21st, 2020, at Al-Zahra Hospital, one of the major teaching hospitals of the Tabriz University of Medical Sciences. Study Population

Inclusion criteria included preterm neonates with gestational age < 37 weeks, confirmed diagnosis of LOS, defined as the onset of symptoms at ≥ 72 hours of life, and a written informed consent form signed by a parent or a legal guardian. Infants with intracerebral hemorrhage, maternal infection, kidney insufficiency, and hypersensitivity to methylxanthine derivatives were excluded from the trial.

Randomization

Infants were randomly assigned to the intervention and control groups using the blocked randomization method with a 1:1 ratio by an independent person who did not participate in the study procedure. A randomization block sheet was prepared, and AABB, ABAB, ABBA, BBAA, BABA, and BAAB codes were allocated to the participants. Each of the sequences is converted to alphabetic and numeric codes. A statistics specialist (PS) generated the allocation sequence, a neonatologist (MH) enrolled the participants based on eligibility criteria, and DB assigned participants to interventions.

Study process

Infants in the intervention group received pentoxifylline 10 mg/kg three times a day for six days in addition to the standard care. Infants in the control group received only the standard care. Pentoxifylline is administered by dissolving ten 400 mg tablets in 200 mL of distilled water to create an oral solution with a 2 mg/mL concentration. This suspension is refrigerated and can be kept for up to three months.

Study outcomes

The study's primary outcomes included hospitalization, CRP negativity, supplemental oxygen therapy duration, and mortality. The occurrence of adverse events was also assessed as the secondary outcome.

Statistical analysis

Data were analyzed using BM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test was utilized for the analysis of the normality of the data. An independent t-test was used for between-group comparison. Data were shown as numbers (%) for categorical variables, mean ± standard deviation (SD) for normal continuous variables, and median (interquartile range (IQR)) for non-normal continuous variables. The independent t-test or Mann–Whitney U test was performed for between-group comparisons. Comparing hospitalization, CRP negativity, and supplemental oxygen therapy duration after adjusting for covariates was conducted using analysis of covariance. Categorical variables were compared between groups using chi-square and/or Fisher's exact tests. Comparing mortality after adjusting for covariates was performed using logistic regression analysis. The p-value under 0.05 was noted to be statistically significant. The effect sizes of study outcomes were also reported using STATA version 17.

Results

Study population

A total of 57 infants were assessed for eligibility. Of them, 47 infants met the inclusion criteria and were randomized to receive either pentoxifylline with the standard care or the standard care alone. Seven infants were excluded due to treatment discontinuation caused by parental withdrawal of consent, early discharge before outcome assessment, and difficulties in administering oral medication. Eventually, 40 infants (20 in each group) completed the study. The flow diagram of the study is shown in Figure 1.

There was no significant difference between the groups regarding demographic characteristics, mothers/infants-related risk factors, use of antenatal steroids, and neonatal resuscitation at birth (Table 1). The most common clinical manifestation of LOS was respiratory distress, shown in all infants. Other clinical manifestations of LOS were also comparable between the groups. During the study period, there was no significant difference regarding antibiotic regimen and surfactant administration between the study groups; however, respiratory support significantly differed between the intervention and control groups (Table 2).

Study outcomes

After adjusting for respiratory support using the bootstrap method, the results demonstrated no significant difference

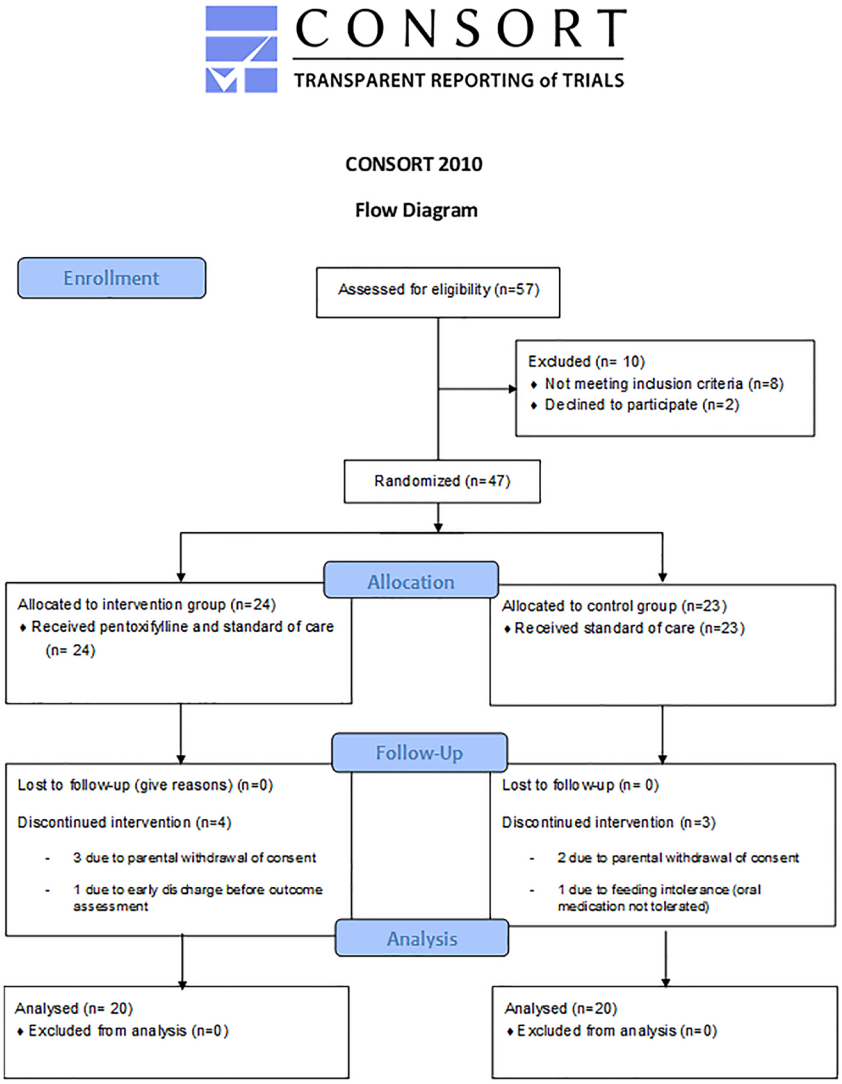

Figure 1. CONSORT flow diagram of the study

between two groups in terms of CRP negativity duration (16.9 ± 13.6 vs. 22 ± 14.2; $P = 0.69$), supplemental oxygen therapy duration (4.7 ± 3 vs. 4 ± 1; $P = 0.94$), hospitalization rate(21.4 ± 14.3 vs. 26.3 ± 14.9; $P = 0.56$), and mortality rate (P = 0.5, using logistic regression analysis) as the primary outcomes (Table 3). Regarding secondary outcomes, oral pentoxifylline was well tolerated, and no treatment-limiting adverse effect was reported in the intervention group during the study period.

Effect size

Effect sizes were calculated to assess the size of the difference between the intervention and control groups. For continuous outcomes, mean differences (MD) values indicated non-significant effect sizes for hospitalization [MD: -4.90, 95% confidence interval (CI), (-13.95, 4.15)] CRP negativity [MD: -5.10, 95% CI, (-13.72, 3.52)], and oxygen therapy duration [MD: 0.70, 95% CI, (-0.69, 2.09)]. The risk ratio (RR) of mortality as categorical outcome, indicated no significant difference between the study groups [RR:1, 95% CI, (0.07, 14.90)] (Table 3).

Discussion

To our knowledge, this is the first randomized clinical trial that looks at the potential of oral pentoxifylline in the treatment of LOS in preterm neonates. The study showed that pentoxifylline 10 mg/kg three times a day for six days had no significant effect on hospitalization, CRP negativity, and supplemental oxygen therapy duration, as well as mortality rate.

A growing body of literature has tested the potential effects of pentoxifylline in neonatal sepsis. One of the most essential proposed pharmacological properties of pentoxifylline in managing neonatal sepsis is its immunomodulatory effects. In this regard, Lauterbach and Zembala showed that administering intravenous 5 mg/kg/h pentoxifylline for 6 hours on 3 successive days could significantly decrease TNF-α in neonates with sepsis. Further clinical trials were designed to evaluate the effects of pentoxifylline on clinical and paraclinical outcomes of neonates with LOS.[11] A double-blind placebo-controlled trial in 29 newborn infants with sepsis showed that while there was no significant difference regarding

Table 1. Demographic and clinical characteristics of infants and mothers

Characteristics	Intervention (n=20)	Control (n=20)	*P* value
Gestational age (week)	32.05± 3.1	31.2±3.1	0.39
Mother age (year)	33.05±6	29.5±7.4	0.11
Infant weight (g)	1784.1±710.3	1773.7±663.9	0.96
Cesarean delivery, n (%)	19 (95%)	16(80%)	0.34
Female sex, n (%)	7 (35%)	9 (45%)	0.40
Apgar1	7.8±1.3	6±1.8	0.30
Apgar5	7.8±2.4	7.8±1.38	0.36
Mother-related risk factors			
Hypertension, n (%)	10 (50)	7 (35)	0.52
Thyroid disorder, n (%)	4 (20)	4 (20)	>0.99
Preeclampsia, n (%)	4 (20)	2 (10)	0.66
Diabetes, n (%)	0 (0)	3 (15)	0.23
Prior infant death, n (%)	0 (0)	1 (5)	>0.99
Infertility history, n (%)	1 (5)	0 (0)	>0.99
Infant-related risk factors			
Multiple pregnancy, n (%)	4 (20)	1 (5)	0.34
Placental abruption, n (%)	3 (15)	3 (15)	>0.99
Umbilical cord disorder, n (%)	1 (5)	2 (10)	>0.99
Premature rupture of the membranes, n (%)	1 (5)	2 (10)	>0.99
Intrauterine growth restriction, n (%)	1 (5)	1 (5)	>0.99
Biophysical profile disorder, n (%)	1 (5)	0 (0)	>0.99
Meconium aspiration, n (%)	2 (10)	0 (0)	0.48
Vaginal bleeding, n (%)	0 (0)	1 (5)	>0.99
Placental Previa, n (%)	0 (0)	1 (5)	>0.99
Use of antenatal steroids			**0.16**
No use, n (%)	6 (30)	6 (30)	
Partial n (%)	5 (25)	10 (50)	
Complete n (%)	9 (45)	4 (20)	
Neonatal resuscitation at birth			**0.06**
Normal care, n (%)	9 (45)	3 (15)	
First steps of revival, n (%)	4 (20)	9 (45)	
Continuous positive airway pressure, n (%)	5 (25)	4 (20)	
Positive pressure ventilation with mask, n (%)	0 (0)	3 (15)	
Positive pressure ventilation with tracheal intubation, n (%)	2 (10)	1 (5)	

An independent t-test was used for between-group comparison. Categorical variable was compared between groups using chi-square and/or Fisher's exact tests.

Table 2. Late-onset sepsis clinical manifestation of treatment

Characteristic	Intervention (n=20)	Control (n=20)	*P* value
Respiratory distress, n (%)	20 (100)	20 (100)	>0.99
Bad color, n (%)	6 (30)	7 (35)	>0.99
Tachypnea, n (%)	2 (10)	7 (35)	0.12
Metabolic acidosis, n (%)	3 (15)	5 (25)	0.6
Leukopenia, n (%)	4 (20)	5 (25)	>0.99
Leukocytosis, n (%)	4 (20)	3 (15)	>0.99
Abdominal distension, n (%)	1 (5)	4 (20)	0.34
Feeding intolerance, n (%)	1 (5)	3 (15)	0.60
Dopamine need, n (%)	3 (15)	1 (5)	0.60
Temperature instability, n (%)	1 (5)	1 (5)	>0.99
Mottled skin, n (%)	1 (5)	0 (0)	>0.99
Pallor, n (%)	0 (0)	1 (5)	>0.99
Respiratory support			0.01
Nasal Continuous Positive Airway Pressure, n (%)	8 (40)	15 (75)	
Non-invasive ventilation, n (%)	1 (5)	3 (15)	
Humidified High-flow nasal cannula, n (%)	6 (30)	2 (10)	
Oxygen incubator, n (%)	5 (25)	0 (0)	
Surfactant administration			0.10
One dose, n (%)	7 (35)	2 (10)	
Two doses, n (%)	4 (20)	8 (40)	
Three doses, n (%)	1 (5)	4 (20)	
Antibiotic regimen			0.36
Amikacin-vancomycin, n (%)	13 (65)	10 (50)	
Amikacin-vancomycin- piperacillin/ tazobactam, n (%)	3 (15)	6 (30)	
Amikacin-vancomycin-ampicillin, n (%)	0 (0)	2 (10)	
Amikacin-vancomycin-meropenem, n (%)	3 (15)	2 (10)	
Ciprofloxacin- piperacillin/tazobactam, n (%)	1 (5)	0 (0)	

Categorical variable was compared between groups using chi-square and/or Fisher's exact tests.

coagulation parameters between the study groups, treatment with pentoxifylline (5 mg/kg/h for 6 hours; for 6 successive days led to a significant decrease in multiple organ dysfunction syndrome ($P=0.037$), hospital stay duration, bleeding ($P=0.0128$) and fresh frozen plasma use ($P=0.003$).A systematic review and meta-analysis of 6 studies with 416 neonates with sepsis also supported the benefits of pentoxifylline on all-cause mortality during hospital stay (RR: 0.57, 95% CI 0.35 to 0.93).[12]

Depending on the onset time, sepsis can be classified as early-onset sepsis (EOS) or LOS. Commonly, EOS refers to sepsis in neonates at or before 72 hours of life, and LOS is defined as sepsis occurring at or after 72 hours of life.[13,14] In addition to the onset of sepsis, there are considerable differences regarding the pathogenesis and management of EOS and LOS.[15] So, it seems that the effects of pentoxifylline in individuals with EOS and LOS could differ.

A series of randomized clinical trials aimed to evaluate the effects of pentoxifylline in individuals with LOS. A double-blind, randomized controlled trial in 120 preterm infants with LOS showed that administration of intravenous 5 mg/kg/h pentoxifylline for 6 hours on 6 successive days had no significant effect on mortality ($P=0.44$), short-term morbidity, and combined mortality and/or short-term morbidity ($P=0.23$).[10] Another double-

Table 3. Study outcomes' parameters

Characteristic	Intervention (n = 20)	Control (n = 20)	*P* value[1]		Effect sizes with 95% CI[2]
Hospitalization (day), mean (SD)	21.4 ± 14.3	26.3 ± 14.9	0.56[3]	0.25	-4.90 [-13.95, 4.15]
CRP negativity (day), mean (SD)	16.9 ± 13.6	22 ± 14.2	0.69[3]	0.15	-5.10 [-13.72, 3.52]
Supplemental oxygen therapy (day), mean (SD)	4.7 ± 3	4 ± 1	0.94[3]	> 0.99	0.70 [-0.69, 2.09]
Death, n (%)	1(5%)	1(5%)	0.5[4]	> 0.99	1 [0.07, 14.90]

[1] Values are presented as mean ± SD or n (%). Continuous variables were compared using independent t-test or Mann–Whitney U test. Categorical variables were compared using chi-square or Fisher's exact test. Adjusted analyses were performed using the bootstrap method for continuous outcomes and logistic regression for mortality.
[2] For continuous outcomes, we used mean difference, and for categorical outcomes, the Risk ratio was calculated.
[3] P value after adjusting for respiratory support using the bootstrap method.
[4] p-value after adjusting for respiratory support using logistic regression analysis.

blinded randomized clinical trial tested the effects of the same dose and duration of pentoxifylline in 80 preterm newborns with LOS. Data showed that pentoxifylline could improve protein C ($P = 0.020$), duration of antimicrobial therapy ($P = 0.001$), duration of hospital stay in survivors ($P = 0.012$), continuous positive airway pressure therapy ($P = 0.03$), and requirement for plasma transfusions ($P = 0.03$).[16]

Despite utilizing the oral form of pentoxifylline in our trial, the administration of this medication at a dose of 30 mg/kg in three divided doses for six days had no significant effects on observed study outcomes, which could be due to the small sample size and a short follow-up period of the study. The lack of significant differences in outcomes may be attributed to the pharmacokinetics of pentoxifylline in neonates. Compared to adults, neonates may exhibit different metabolic profiles, resulting in variations in drug efficacy. Furthermore, the sustained-release formulation used in this study may have been altered by crushing the tablets to create an oral suspension, which could have led to increased plasma concentrations and potentially erratic drug levels.

Additionally, the relatively low dose used in the trial may not have been sufficient to achieve optimal therapeutic effects, particularly given the short duration of treatment. These factors may have contributed to the observed outcomes.

Data regarding pharmacokinetic differences of oral and intravenous pentoxifylline in neonates were limited, but recent studies in animals compared the bioavailability of whole and crushed tablets. The findings indicate that the relative bioavailability of pentoxifylline is equivalent in both forms, with no significant differences reported. However, the metabolic profile of pentoxifylline does appear to be influenced by the route of administration. Notably, the ratios of areas under the curve (AUC) for pentoxifylline and its metabolite differ significantly between oral and intravenous dosing regimens.[17] It is worth mentioning that pentoxifylline is only available in sustained-release tablet form. Crushing this formulation can lead to increased maximum plasma concentrations and a decrease in the time to reach maximum concentrations, resulting in higher plasma levels and potential dose-related adverse effects such as nausea and dizziness.[18] Conversely, in our study, pentoxifylline was well-tolerated without any significant adverse events being reported which may be attributed to the low dose administered.

The heterogeneity of the LOS population presents a significant consideration in treatment outcomes. The presence of varying causative pathogens, underlying risk factors, and baseline health status may influence the effectiveness of interventions. To address this concern, additional secondary parameters were included to ensure baseline comparability between the intervention and control groups. These parameters comprised demographic characteristics, maternal and infant risk factors, as well as clinical manifestations. However, the small sample size limited addressing all confounding variables.

Despite well-absorbed pentoxifylline being widely used in clinical practice for many years in NICUs and clinical trials, data regarding the pharmacokinetics of pentoxifylline in this population are limited. In Salman et al. pilot pharmacokinetic trial, 30 mg/kg per 6 hours was well tolerated and without treatment-limiting adverse effects.[19] Accordingly, in most clinical trials in the field of neonatal LOS, intravenous 5 mg/kg/h pentoxifylline for 6 hours on 6 successive days was used. There are also uncertainties regarding the optimal dose, duration, and even route of administration of pentoxifylline in the management of preterm infants with LOS. In the pentoxifylline optimal dose finding ongoing trial in preterm neonates with LOS, the starting dose of pentoxifylline is 30 mg/kg/d.[20] In the treatment of Kawasaki disease, the recommended dose of oral pentoxifylline in infants with ≥ 2 months is 20 mg/kg/d in three divided doses.[21] Our study was the first trial to evaluate the effects of oral pentoxifylline in the management of LOS. The dose of pentoxifylline in our study was based on its intravenous dose in clinical trials and oral dose in clinical practice.

The clinical implications of the current study should be mentioned. It is the first trial to investigate the oral administration of pentoxifylline preterm neonates, offering a less invasive treatment option than intravenous therapy. Additionally, the findings contribute to the growing body of evidence on the role of pentoxifylline neonatal sepsis, highlighting the challenges associated with clinical use of this drug in preterm neonates. Future research is still warranted on identifying the optimal dose and duration of pentoxifylline therapy in neonates, as

well as comparing oral and intravenous routes in larger, multicenter trials. Pharmacokinetic studies are also needed to identify the metabolism and bioavailability of oral pentoxifylline this population.

Limitations

Because of the following limitations, the results of randomized clinical trials should be interpreted with caution. First, the current study is a pilot trial with a relatively small sample size, and may not be sufficient to explore the mortality outcomes. Second, the precise dose and duration of pentoxifylline in the treatment of LOS are unknown and must be clarified by ongoing trials. Third, we did not use a placebo to reduce potential treatment bias due to practical limitations. Future studies should consider the use of a placebo-controlled design to minimize cofounding bias.

Conclusion

Among preterm neonates with LOS, adding pentoxifylline 10 mg/kg three times a day for six days to the standard care had no significant effect on hospitalization, CRP negativity, and supplemental oxygen therapy duration, as well as mortality rate compared with standard care alone. Administration of pentoxifylline in preterm neonates with LOS was well tolerated without treatment-limiting adverse effects.

Acknowledgments

The authors acknowledge the Al-Zahra Hospital of Tabriz University of Medical Sciences.

Authors' Contribution

Conceptualization: Elnaz Shaseb, MohammadBagher Hosseini.
Data curation: Elnaz Shaseb, Donya Behzadi Mohammadi.
Formal analysis: Parvin Sarbakhsh.
Investigation: Parvin Sarbakhsh, Sajad Khiali.
Methodology: Elnaz Shaseb, Parvin Sarbakhsh.
Project administration: Elnaz Shaseb.
Resources: Elnaz Shaseb, MohammadBagher Hosseini.
Software: Parvin Sarbakhsh.
Supervision: MohammadBagher Hosseini.
Validation: Elnaz Shaseb, Donya Behzadi Mohammadi.
Visualization: Parvin Sarbakhsh, Sajad Khiali.
Writing-original draft: Sajad Khiali, Hila Asham.
Writing-review & editing: Sajad Khiali, Hila Asham.

Competing Interests

None.

Data Availability Statement

Data will be made available on request from the corresponding author.

Ethical Approval

This study was approved by the ethics committee of Tabriz University Medical Sciences (IR.TBZMED.REC.1398.996) and was verified in the Iranian Clinical Trials Registry Platform with the identification IRCT20180404039187N7. All patients gave written informed consort forms before enrollment. The study was in accordance with the Declaration of Helsinki and later revisions of ethical principles for medical research.

Funding

None.

References

1. Cortese F, Scicchitano P, Gesualdo M, Filaninno A, De Giorgi E, Schettini F, et al. Early and late infections in newborns: where do we stand? A review. Pediatr Neonatol. 2016;57(4):265-73. doi: 10.1016/j.pedneo.2015.09.007.
2. Ramasethu J. Prevention and treatment of neonatal nosocomial infections. Matern Health Neonatol Perinatol. 2017;3:5. doi: 10.1186/s40748-017-0043-3.
3. Greenberg RG, Kandefer S, Do BT, Smith PB, Stoll BJ, Bell EF, et al. Late-onset sepsis in extremely premature infants: 2000-2011. Pediatr Infect Dis J. 2017;36(8):774-9. doi: 10.1097/inf.0000000000001570.
4. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics. 2002;110(2 Pt 1):285-91. doi: 10.1542/peds.110.2.285.
5. Tsai MH, Hsu JF, Chu SM, Lien R, Huang HR, Chiang MC, et al. Incidence, clinical characteristics and risk factors for adverse outcome in neonates with late-onset sepsis. Pediatr Infect Dis J. 2014;33(1):e7-13. doi: 10.1097/INF.0b013e3182a72ee0.
6. Speer EM, Dowling DJ, Ozog LS, Xu J, Yang J, Kennady G, et al. Pentoxifylline inhibits TLR- and inflammasome-mediated in vitro inflammatory cytokine production in human blood with greater efficacy and potency in newborns. Pediatr Res. 2017;81(5):806-16. doi: 10.1038/pr.2017.6.
7. Zhang M, Xu YJ, Mengi SA, Arneja AS, Dhalla NS. Therapeutic potentials of pentoxifylline for treatment of cardiovascular diseases. Exp Clin Cardiol. 2004;9(2):103-11.
8. Weitz JI, Byrne J, Clagett GP, Farkouh ME, Porter JM, Sackett DL, et al. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. Circulation. 1996;94(11):3026-49. doi: 10.1161/01.cir.94.11.3026.
9. Harris E, Schulzke SM, Patole SK. Pentoxifylline in preterm neonates: a systematic review. Paediatr Drugs. 2010;12(5):301-11. doi: 10.2165/11532600-000000000-00000.
10. Shabaan AE, Nasef N, Shouman B, Nour I, Mesbah A, Abdel-Hady H. Pentoxifylline therapy for late-onset sepsis in preterm infants: a randomized controlled trial. Pediatr Infect Dis J. 2015;34(6):e143-8. doi: 10.1097/inf.0000000000000698.
11. Lauterbach R, Zembala M. Pentoxifylline reduces plasma tumour necrosis factor-alpha concentration in premature infants with sepsis. Eur J Pediatr. 1996;155(5):404-9. doi: 10.1007/bf01955273.
12. Pammi M, Haque KN. Pentoxifylline for treatment of sepsis and necrotising enterocolitis in neonates. Cochrane Database Syst Rev. 2023;6(6):CD004205. doi: 10.1002/14651858.CD004205.pub4.
13. Hornik CP, Fort P, Clark RH, Watt K, Benjamin DK Jr, Smith PB, et al. Early and late onset sepsis in very-low-birth-weight infants from a large group of neonatal intensive care units. Early Hum Dev. 2012;88(Suppl 2):S69-74. doi: 10.1016/s0378-3782(12)70019-1.
14. Schuchat A. Neonatal group B streptococcal disease--screening and prevention. N Engl J Med. 2000;343(3):209-10. doi: 10.1056/nejm200007203430310.
15. Bulkowstein S, Ben-Shimol S, Givon-Lavi N, Melamed R, Shany E, Greenberg D. Comparison of early onset sepsis and community-acquired late onset sepsis in infants less than 3 months of age. BMC Pediatr. 2016;16:82. doi: 10.1186/s12887-016-0618-6.
16. El Sebaie D, Mansi Y, Nasr AS, Khairy SA, Tosson A. Effect of pentoxifylline on late-onset sepsis and protein c level in preterm neonates: a double-blinded randomized controlled

trial. Egypt J Hosp Med. 2022;89(1):4930-7. doi: 10.21608/ejhm.2022.260862.
17. Beermann B, Ings R, Månsby J, Chamberlain J, McDonald A. Kinetics of intravenous and oral pentoxifylline in healthy subjects. Clin Pharmacol Ther. 1985;37(1):25-8. doi: 10.1038/clpt.1985.6.
18. Cleary JD, Evans PC, Hikal AH, Chapman SW. Administration of crushed extended-release pentoxifylline tablets: bioavailability and adverse effects. Am J Health Syst Pharm. 1999;56(15):1529-34. doi: 10.1093/ajhp/56.15.1529.
19. Salman S, Hibbert J, Page-Sharp M, Manning L, Simmer K, Doherty DA, et al. Effects of maturation and size on population pharmacokinetics of pentoxifylline and its metabolites in very preterm infants with suspected late-onset sepsis or necrotizing enterocolitis: a pilot study incorporating clinical outcomes. Br J Clin Pharmacol. 2019;85(1):147-59. doi: 10.1111/bcp.13775.
20. Kurul S, Taal HR, Flint RB, Mazela J, Reiss IKM, Allegaert K, et al. Protocol: Pentoxifylline optimal dose finding trial in preterm neonates with suspected late onset sepsis (PTX-trial). BMC Pediatr. 2021;21(1):517. doi: 10.1186/s12887-021-02975-8.
21. Best BM, Burns JC, DeVincenzo J, Phelps SJ, Blumer JL, Wilson JT, et al. Pharmacokinetic and tolerability assessment of a pediatric oral formulation of pentoxifylline in Kawasaki disease. Curr Ther Res Clin Exp. 2003;64(2):96-115. doi: 10.1016/s0011-393x(03)00018-3.