Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2019;44(4):1412-1417
DOI: 10.17826/cumj.605903

ARAŞTIRMA / RESEARCH

Pentoxyfilline treatment in nosocomial sepsis of preterm infants

Preterm bebeklerin nozokomiyal sepsisinde pentoksifilin tedavisi

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Cukurova Medical Journal 2019;44(4):1412-1417.

Abstract

Purpose: Nosocomial sepsis is the most common acquired infection. Despite appropriate antibiotic treatment, mortality and morbidity of sepsis are still high. We aimed to evaluate the effect of pentoxifylline on prognosis of neonatal nosocomial sepsis in premature infants hospitalized in the neonatal intensive care unit.

Materials and Methods: Eighty newborns diagnosed as nosocomial sepsis were included in this study. Forty of them received pentoxifylline treatment in addition to antibiotics, while the other 40 did not receive additional treatment and formed the control group. The sex, mode of delivery, gestational age, birth weight, Apgar scores at the 1st and 5th minutes, surfactant therapy, ventilator therapy and presence of early onset sepsis were compared between the case group and the control.

Results: There was no statistical difference between groups according to gestational week, gender, birth weight, mortality, neutrophil count or procalcitonin level at the time of diagnosis. Also, there was not any statistical difference according to duration of hospitalization between the bronchopulmonary dysplasia or necrotizing enterocolitis groups.

Conclusion: Pentoxifylline has no significant impact on mortality and morbidity of preterm nosocomial sepsis.

Key words: Pentoxifylline, premature, sepsis

Öz

Amaç: Nozokomiyal sepsis, hastane kaynaklı kazanılmış infeksiyonlar arasında en sık olanıdır. Uygun antibiyotik tedavisine rağmen sepsisin mortalitesi ve morbiditesi hala yüksektir. Bu nedenle diğer tedavi yöntemleri hala aranmaktadır. Yenidoğan yoğun bakım ünitesinde yatan prematüre bebeklerde pentoksifilinin neonatal nozokomiyal sepsisin prognozu üzerine etkisini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu çalışmaya nozokomiyal sepsis tanısı konan 80 yenidoğan dahil edildi. Bunların 40'ı antibiyotiklere ek olarak pentoksifilin tedavisi alırken, diğer 40'ı almadı ve kontrol grubunu oluşturdu. Gebelik yaşı, doğum ağırlığı, 1. ve 5. dakikadaki Apgar skorları, doğum şekli, cinsiyeti, surfaktan tedavisi, ventilatör tedavisi ve erken başlangıçlı sepsis varlığı vaka grubuyla kontrol arasında karşılaştırıldı.

Bulgular: Gruplar arasında tanı anında gebelik haftası, cinsiyet, doğum ağırlığı, mortalite, nötrofil sayısı veya prokalsitonin düzeylerine göre istatistiksel bir fark yoktu. Ayrıca, hastanede kalış süresi, bronkopulmonerdisplazi veya nekrotizan enterokolit gelişmesine göre de gruplar arasında istatistiksel bir fark yoktu.

Sonuç: Pentoksifilin, preterm nozokomiyal sepsisin mortalitesi ve morbiditesi üzerinde önemli bir etkiye sahip değildir.

Anahtar kelimeler: Pentoksifilin, prematüre, sepsis

INTRODUCTION

Because of the technological development in the neonatal intensive care, the life span of very premature neonates is increasing. Consequently, nosocomial infections are increasing in those babies[1]. Nosocomial sepsis, which occurs 72-96 hours after hospitalization, is the most common acquired infection[2,3].

Empirical antibiotherapy should be started as soon as possible after having samples for cultures in a suspected neonate. Mortality and morbidity of neonatal sepsis is still high despite the use of effective antimicrobial agents[4]. The increasing use of antimicrobials has led to an increase in antibiotic

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Geliş tarihi/Received: 04.05.2019 Kabul tarihi/Accepted: 30.07.2019 Çevrimiçi yayın/Published online: 16.09.2019

resistance. Therefore, supportive therapies like intravenous immunoglobulins (IVIG), colony stimulating factors, lactoferrin and selenium were tried[5]. Microorganisms causing sepsis activates inflammatory mediators as well as proinflammatory cytokines like tumor necrosis factor alpha (TNF-α), interleukin 1(IL-1), interleukin 6 (IL-6)[6]. Increase of the TNF levels in both plasma and serum is correlated with severity of the sepsis[7]. Agents that control inflammation, such as Pentoxifylline (PTX), a phosphodiesterase inhibitor, can improve results. Hence, pentoxifylline is being increasingly employed in neonatal sepsis treatment as an immunomodulatory agent[8].

Current evidence regarding the efficacy of PTX as an adjuvant therapy in sepsis is not conclusive. Randomized trials have reported conflicting outcomes[9-11]. In this study, we investigate the effect of PTX as a supportive addition to antibiotic treatment on neonatal nosocomial sepsis in premature infants hospitalized in our Neonatal Intensive Care Unit (NICU).

MATERIALS AND METHODS

Eighty premature neonates diagnosed as nosocomial sepsis that were hospitalized in Çukurova University Balcalı Hospital 3rd level NICU between January 2011-December 2013 are enrolled in this study, retrospectively. This study has a matched case control study design. We matched study cases with control cases for gestational age (week), weight at birth (g), Apgar scores at 1st and 5th minutes, type of delivery (C/S), sex, surfactant treatment, ventilatory treatment and early onset sepsis. Preterm infants born before 38 gestational weeks were included. Exclusion criteria of the study were determined as major congenital anomalies, term neonates and no nosocomial sepsis. We included 40 newborns treated with PTX adjuvant to antibiotics (PTX group) and other 40 who did not and formed the control group.

The diagnosis of nosocomial sepsis was made after 96 hours of hospitalization when at least two of the following findings were present; (a) unstable temperature (hyperthermia hypothermia); (b) cardiovascular symptoms (tachycardia, bradycardia, poor perfusion, hypotension); (c) respiratory symptoms (intercostal retractions, apnea, tachypnea, cyanosis); (d) neurological symptoms (lethargy, seizures, hypotonia); and (e) gastrointestinal symptoms (abdominal distension, feeding intolerance)[12,13].

As the neonate was diagnosed as clinical sepsis, after having laboratory investigations such as whole blood count, procalcitonin, blood culture, urinalysis, radiological investigations, empirical vancomycin and meropenem treatment started according to appropriate dosage for gestational weeks and PTX (Trental, Sanofi-Aventis, Istanbul, Turkey) was given simultaneously with or just half an hour before the first dose of antibiotics intravenously at a dose of 5 mg/kg/h for 6 hours for 5 successive days.

In our clinic, staphylococcus epidermidis and gram-negative basils are predominante microorganisms in nosocomial sepsis, so we started vancomycin and meropenem as empirical agents[14]. At 3rd day of diagnosis complete blood count and procalcitonin levels were evaluated for need of further supportive therapy and the response to treatment.

Antibiotics were continued up to at least 14-21 days in infants with culture proven sepsis. If the blood culture at the time of diagnosis is negative (clinic sepsis) the duration of antibiotics was 10 days. At the end of the treatment, demographic data of the neonates, gestational weeks, birth weights, maternal age, blood culture results, response to treatment were evaluated.

Bell's classification was used to stage necrotizing enterocolitis (NEC)[15]. Bronchopulmonary dysplasia (BPD) was described as oxygen dependency at a postconceptional age of 36 weeks for infants with a gestational age ≤ 32 weeks, and at 56 days for those with a gestational age > 32 weeks[16]. The primary outcome measure was mortality due to sepsis and the secondary outcome parameters were duration of hospitalization, BPD and NEC.

Parents were informed about the treatment. None of the neonates enrolled in this study got intravenous immunoglobulins treatment during sepsis therapy. Ethics committee approval was obtained for the study in the meeting of Çukurova University Noninvasive Clinical Research Ethics Committee with decision No. 90 on June 5, 2019. Since this was a retrospective study, voluntary/ patient consent was not required.

Statistical analysis

All analyses were performed using IBM SPSS Statistics Version 19.0 (SPSS, Chicago, IL) statistical

software package. Categorical variables were expressed using counts and percentage whereas continuous variables were summarized in mean, ± standard deviation, median, min and max values. The t-test was used to compare two group means. the Mann-Whitney test was used for non-normally distributed variables. In all tests, p-value < 0.05 was considered to be statistically significant.

RESULTS

Eighty premature infants accepted in this study. Mean gestational week and birth weight of the patients were 29.5±3.2(25-38) weeks and 1318.0±542.6(540-3040) gram respectively. Seventy-five (93.75%) of the patients had appropriate birth weight with the gestational age. Apgar scores at 1st and 5th minutes were 5.11±1.5 (1-9) and 7.39±1.3 (4-10), respectively. Ten patients (12.5%) were outborn. Incidence of resuscitation at birth was the same at two groups. Fiftyfour patients were discharged. Demographic properties of the two groups are in Table 1.

Thirty-seven (92.5%) infants in the PTX-group had a birth weight that was appropriate for their gestational age. Two babies were born outside of our hospital while the others were inborn in the PTX-group. In PTX group, blood cultures were negative in 14 babies (35%) while 16 (40%) had gram negative bacteria (K oxytoca in nine neonates, S marcensis in three, E coli in one, E cloaca in one, P aeuroginosa in one and A baumanii in one neonate), eight (20%) had gram positive bacteria (S aureus in two, S epidermidis in two and S hominis in one neonate) and 2 (5%) had fungal growth in blood cultures. Twenty- eight (70%) babies of PTX group were discharged and 12 neonates were died (Three of them were died during sepsis attack and nine of them were died due to some other reasons after the attack was over). Five neonates were died before the 28th day of life. NEC was diagnosed in 7 (18.9%) patients in PTX group. BPD was evaluated in 35 infants in PTX group because 5 infants were discharged before 28th day of life and 14/35 (40%) had BPD. Mean duration of hospitalization was 51.0 ± 34.8 (10-160) days in PTX group (Table).

Table-1. Demographic and clinical data of the patients among the groups

	PTX group N=40	Control group N=40	p
Gestational week (week) mean ± SD (min-max)	29.5 ± 3.3 (25-37)	29.4 ± 3.1 (25-37)	>0.05
Birth weight (gram) mean ± SD (min-max)	1317.0 ± 543.1 (540-3040)	1319.0 ± 548.9 (540-3000)	>0.05
Male	22 (55%)	22 (55%)	>0.05
Cesarean Section delivery	38 (95%)	38 (95%)	>0.05
Early onset sepsis (+)	35 (87.5%)	34 (85%)	>0.05
Nosocomial sepsis diagnosis time (day) mean ± SD (min-max)	15.2 ± 11.5 (4-57)	15.2 ± 11.6 (4-60)	>0.05
Blood Culture (+)	26 (65%)	28 (70%)	>0.05
Neutrophil Count at the time of diagnosis (/mm3) mean+/-SD Median (min-max)	12509.3 ± 9499.1 9380 1410-52300	12388.8 ± 9323.3 10000 1500-53000	>0.05
Neutrophil Count at 3rd day of diagnosis (/mm3) mean+/-SD Median (min-max)	9612.5 ± 4620.4 9500 2500-25000	9197.5 ± 5126.8 8000 3400-25000	>0.05
Procalcitonin at the time of diagnosis (ng/dl) Median (min-max)	24.6 ± 27.8 12.35 0.28-100	24.8 ± 27.6 14 0.20-100	>0.05
Procalcitonin at 3rd day of diagnosis (ng/dl) Median (min-max)	9.2 ± 10.6 6 0.1-42	6.8 ± 8.07 3 0.1-30	>0.05
Exitus due to sepsis attack	3 (7.5%)	6 (15%)	>0.05
BPD	14/35 (40%)	17/37 (45.9%)	>0.05
NEC	7 (18.9%)	9 (22.5%)	>0.05
Hospitalization duration(day) mean ± SD (min-max)	51.0 ± 34.8 41 (10-160)	51.1 ± 33.6 41.5 (11-148)	>0.05

**BPD: Bronchopulmonary dysplasia ¶NEC: Necrotising enterocolitis *PTX: Pentoxifylline

Thirty-six (90%) of the babies in the control group had a birth weight that was appropriate for their gestational age. Six babies were out born while the others were inborn in control group. In control group, blood cultures were negative in 12 babies (30%) while 17 (42.5%) had gram negative bacteria (K oxytoca in ten neonates, S marcensis in three, E coli in one, E cloacae in one, P aeuroginosa in one and A baumanii in one neonate), ten (25%) had gram positive bacteria (S hominis in five, S epidermitis in three and S aureus in two neonate) and one (2.5%) had fungal growth in blood cultures. Twenty- six (65%) babies of control group were discharged and 14 neonates were died (six were died during sepsis attack and eight were died due to some other reasons after attack was over). NEC was diagnosed in 9 (22.5%) patients in control group. BPD was evaluated in 37 infants in control group because 3 infants were discharged before 28th day of life and 17/37 (45.9%) had BPD. Mean duration of hospitalization was 51.1± 33.6 (11-148) days.

No statistically significant difference was detected between the groups in terms of mortality, neutrophil count or procalcitonin level, at the time of diagnosis or at the 3rd day after initial diagnosis ($p>0.05$) (Table). BPD and NEC were not found to be different between the groups. Mortality due to a sepsis attack was seen more in the control group but this was not statistically significant.

DISCUSSION

Neonatal sepsis is the most common cause of neonatal death and it is significantly higher in developing countries (6.5 to 38 per 1000 live births)[17]. Nosocomial infections (onset after 72 hours of hospitalization) increases the use of medical resources, duration of hospitalization, as well as increases cost of treatment so that it has an important impact on the healthcare system in both developed and developing countries[18].

The increasing information in the literature on the pathophysiological role of cytokines in septic shock has increased the efforts to control their synthesis and their action in clinical conditions. TNF plays an important role in the pathogenesis of sepsis and septic shock[19]. Suppression of the biosynthesis of TNF as an adjuvant therapy might therefore be one of the strategies in the management of sepsis[20,21].

Pentoxifylline (PTX) has various effects on the immune system, but the predominant effect is the inhibition of the release of proinflammatory cytokines[22]. A few studies have been performed to determine the relationship between sepsis and tumor necrosis factor (TNF) and interleukins (IL), but the outcomes are contradictory[11,23].

PTX has anti-inflammatory properties through inhibition of proinflammatory cytokines, such as TNF-α, lowers blood viscosity and improves microcirculation and tissue perfusion[9]. Recent studies have evaluated the potential value of PTX as an adjuvant therapy in nosocomial sepsis, but the current evidence is weakened by methodological issues in the analyzed studies, and therefore, the routine use of PTX in nosocomial sepsis has not been recommended yet[24].

Lauterbach et al[14] found that PTX significantly affects the synthesis of TNF and IL-6, in addition to reducing the mortality rate in premature infants diagnosed with sepsis. In another study, Casey et al. did not find any difference between the groups receiving PTX and not-receiving PTX, in terms of leukocyte count and the levels of serum TNF alpha and IL-6, CRP [19]. We also did not find any statistical difference in neutrophil count or procalcitonin levels at the time of diagnosis and on the 3rd day of diagnosis between groups. We did not check the IL-6 and TNF alpha levels during sepsis.

A recent Cochrane review has showed that there is a significant reduction in mortality due to any cause during their hospitalization, in neonates with sepsis who had PTX as an adjunct treatment to antibiotic therapy, compared with neonates with sepsis who received placebo as an adjunct treatment[25]. We have demonstrated that, in preterm infants with a suspected or confirmed nosocomial sepsis diagnosis, PTX does not influence mortality. This finding is contradictory to the reported results of other studies in the literature[8,11].

The main limitations of this study were being a case control with small sample size and absence of inflammatory markers such as IL-6 or TNF assessment before and after the treatment. Additionally, this study did not compose all patients with confirmed sepsis in the study period.

There are some limitations in this study. In our study we didn't include healthy control group because of the ethical problems. The study design is retrospective, the sample size of the study is small and did not evaluate long-term neurodevelopmental

outcomes. Prospective studies with increased sample size are required to obtain more reliable results.

PTX has no significant impact on mortality and morbidity of preterm nosocomial sepsis. Some other larger studies including new therapies adjuvant to antibiotics alone or in combination with PTX might support the treatment of nosocomial sepsis.

Yazar Katkıları: Çalışma konsepti/Tasarımı: FÖ, MS, HYY; Veri toplama: MKM, HYY; Veri analizi ve yorumlama: MKM, FÖ; Yazı taslağı: MKM, FÖ; İçeriğin eleştirel incelenmesi: MS, HYY, FÖ; Son onay ve sorumluluk: MKM, FÖ, HYY, MS; Teknik ve malzeme desteği: MKM; Süpervizyon: FÖ, MS; Fon sağlama (mevcut ise): yok.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.
Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.

Author Contributions: Concept/Design : FÖ, MS, HYY; Data acquisition: MKM, HYY; Data analysis and interpretation: MKM, FÖ; Drafting manuscript: MKM, FÖ; Critical revision of manuscript: MS, HYY, FÖ; Final approval and accountability: MKM, FÖ, HYY, MS; Technical or material support: MKM; Supervision: FÖ, MS; Securing funding (if available): n/a.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support

REFERENCES

1. Carey AJ, Saiman L, Polin RA. Hospital-aquired infections in the NICU: epidemiology for the new millennium. Clin Perinatol. 2008;35:223-49.
2. Edwards MS, Baker CJ. Sepsis in the newborn. In: Krugman's Infectious Diseases of Children. 11th ed. (Eds AA Gershon, PJ Hotez, SL Katz)545-61.: Philadelphia, Mosby, 2004.
3. Harrison GJ. Infections of the fetus and newborn. In Textbook of Pediatric Infectious Diseases. 7th ed. Vol. 1 (Eds RD Feigin, JD Cherry, G Demmler, S Kaplan, W Steinbach, P Hotez):867-901. Philadelphia, Saunders, 2014.
4. Ferrieri P, Wallen LD. Neonatal bacterial sepsis. In Avery's Diseases of the Newborn. 9th ed. (Eds CA Gleason, SU Devaskar):538-50. Philadelphia, Elsevier, 2012.
5. Bajcetic M, Spasic S, Spasojevic I. Redox therapy in neonatal sepsis: reasons, targets, strategy, and agents. Shock. 2014;42:179-84.
6. Damas P, Canivet JL, Groot DD, Vrindts Y, Albert A, Franchimond P, Lamy M. Sepsis and serum cytokine concentrations. Crit Care Med. 1997;25:405-12.
7. Casey LC. Immunologic response to infection and its role in septic shock. Crit Care Clin. 2000;16:193-213.
8. Ali W, Ahmed P, Bhat AM, Mushtaq S. Pentoxifylline in treatment of sepsis of premature neonates. JK Pract. 2006;13:204-07.
9. Harris E, Schulzke SM, Patole SK. Pentoxifylline in preterm neonates: a systematic review. Paediatr Drugs. 2010;12:301–11.
10. Lauterbach R, Zembala M. Pentoxifylline reduces plasma tumour necrosis factor-alpha concentration in premature infants with sepsis. Eur J Pediatr. 1996;155:404–09.
11. Lauterbach R, Pawlik D, Kowalczyk D, Ksycinski W, Helwich E, Zembala M. Effect of the immunomodulating agent, pentoxifylline, in the treatment of sepsis in prematurely delivered infants: a placebo-controlled, double-blind trial. Crit Care Med. 1999;27:807-14.
12. Kuzniewicz MW, Puopolo KM, Fischer A, Walsh EM, Li S, Newman TB et al. A quantitative, risk-based approach to the management of neonatal early-onset sepsis. JAMA Pediatr. 2017;171:365-71.
13. Akdag A, Dilmen U, Haque K, Dilli D, Erdeve Ö, Gokmen T. Role of pentoxifylline and/or IgM-enriched intravenous immunoglobulin in the management of neonatal sepsis. Am J Perinatol. 2014;31:905-12.
14. Yapicioglu H, Satar M, Ozcan K, Narli N, Özlü F, Sertdemir Y et al. A 6-year prospective surveillance of healthcare-associated infections in a neonatal intensive care unit from southern part of Turkey. J Paediatr Child Health. 2010;46:337-42.
15. Walsh MC, Kliegman RM. Necrotizing enterocolitis: Treatment based on staging criteria. Pediatr Clin North Am. 1986;33:179-201.
16. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001;163:1723-9.
17. Zaidi AK, Huskins WC, Thaver D, Bhutta ZA, Abbas Z, Goldman DA. Hospital-acquired neonatal infections in developing countries. Lancet. 2005;365:1175-88.
18. Kawagoe JY, Segre CAM, Pereira CR, Cardosa MF, Silva CV, Fukushima JT. Risk factors for nosocomial infections in critically ill newborns: A 5-year prospective cohort study. Am J Infect Control. 2001;29:109-14.
19. Casey LC, Balk RA, Bone RC. Plasma cytokine and endotoxin levels correlate with survival in patients with the sepsis syndrome. Ann Intern Med. 1993;119:771-8.
20. Ng PC, Li K, Wong RP, Chui K, Wong E, Li G et al. Proinflammatory and anti-inflammatory cytokine responses in preterm infants with systemic infections. Arch Dis Child Fetal Neonatal Ed. 2003;88:209-13.
21. Harris MC, D'Angio CT, Gallagher PR, Kaufman D, Evans J, Kilpatrick L. Cytokine elaboration in critically ill infants with bacterial sepsis, necrotizing enterocolitis or sepsis syndrome: correlation with clinical parameters of inflammation and mortality. J Pediatr. 2005;147:462–8.
22. Mandi Y, Farkas G, Ocsovszky I, Nagy Z. Inhibition of tumor necrosis factor production and ICAM-1 expression by pentoxifylline: beneficial effects in sepsis syndrome. Res Exp Med. 1995;195:297-307.

23. Selim K, Hüseyin C, İbrahim KH, Hasan BU, Kazim U, Hüseyin K. Effect of pentoxifylline on tumor necrosis factor-alpha and interleukin-6 levels in neonatal sepsis. Med J Malaysia. 2004;59:391-4.
24. Shabaan AE, Nasef N, Shouman B, Nour I, Mesbah A, Abdel-Hady H. Pentoxifylline therapy for late sepsis in preterm Infants, A randomized control trial. Pediatr Infect Dis J. 2015;34:145-8.
25. Pammi M, Haque KN. Pentoxifylline for treatment of sepsis and necrotizing enterocolitis in neonates. Cochrane Database Syst Rev. 2015;(3):CD004205.