Journal of Neonatology and Pediatric Care

ScitechJournals

Open Access

May Pentoxifylline Protect Immature Brain Against Disorders Induced By Inflammatory Response In Neonatal Sepsis?

Keywords

Sepsis • Inflammatory response • Brain development • Preterm infant • Interleukine-6 • Pentoxifylline

Short Communication

Ryszard Lauterbach[1]* and Dorota Pawlik[2]

[1,2]Department of Neonatology Jagiellonian University Medical College, Kraków, Poland

***Correspondence:** Ryszard Lauterbach, Department of Neonatology Jagiellonian University Medical College, Kraków, Poland; E-mail: ryszard@lauterbach.pl

Received: 22 November 2023; **Accepted:** 20 December 2023; **Published:** 28 December 2023

Introduction

Prematurity is a chronic hyperinflammatory state when compared to the inflammatory response in adulthood. Even in the absence of disease, the inflammatory reaction is more robust with preterm infants mounting cytokine levels that far exceed those in adults with similar insults. Unregulated inflammatory response is partially due to an increase in production of proinflammatory mediators but is also due to the lack of negative regulator [1].

It is now widely accepted that inflammation interferes with neuronal migration and differentiation. It may also disturb the synaptogenesis [2]. The consequences of the inflammatory episodes might be disorders of brain development as observed in preterm infants. Postnatal bacterial infections, regardless of the results of the blood cultures, are generally accepted as an important risk factor that may cause widespread abnormalities of brain development in premature infants [3]. Moreover, it was found that inflammatory response due to sepsis may impair the process of myelinization and in turn either disrupts the white matter tissue development, or inhibits brain growth, which increases the risk of attentional performance in preterm infants [4]. Recently, Giordano and coauthors [5] suggested that neonatal sepsis might be a risk factor for behavioral abnormalities observed at the age of 5 years in former very low birth weight infants. These infants displayed a more frequently elevated risk for depression, anxiety, and higher than normal emotional reactivity, as well as attention deficits. It was also found that necrotizing enterocolitis triggered a systemic inflammatory response that might result in neurodevelopmental disorders. A significant number of studies showed that up to 45% of children from the infants who survived necrotizing enterocolitis, presented neurodevelopmental impairment [6].

At this point, the question arises whether we should obligatorily enter an anti- inflammatory medicine into the treatment of neonatal sepsis to lessen the risk of immature brain injury. The steroids with their evident and widely recognized adverse effects on the development of the immature brain may be acceptable exclusively in therapy of the most severe stages of sepsis. Until now, there is no alternative method for the limitation of hyperinflammatory response observed in septic preterm neonates. In this case, the promising candidate, which exerts several antioxidant and anti- inflammatory activities seems to be pentoxifylline (PTX), a methylxanthine derivative, a non-specific phosphodiesterase inhibitor. This drug is approved and widely available in most countries as a generic medication. PTX is approved to treat intermittent claudication with the ability to decrease blood viscosity, increase erythrocyte flexibility, and increase tissue oxygen concentration. A considerable number of studies demonstrated that PTX reduced serum concentrations of the inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6 [7]. Moreover, PTX showed preservation of proper endothelial function and coagulation activity in sepsis [8]. The results of the

latest meta-analysis on intravenous administration of PTX as an adjunct to antibiotic therapy of sepsis in neonates were published in June 2023 [9]. The authors analyzed data obtained from six randomized controlled trials (RCT) with 416 neonates. In conclusion, low-certainty evidence was found that adjunct PTX therapy in neonatal sepsis decreased mortality and length of hospitalization. Moreover, the authors maintained that no adverse effects of PTX administration were observed. However, in none of these six RCTs, the neurodevelopment of preterm infants after survival of sepsis was evaluated at the subsequent age of life and no comparison of infants treated to those untreated with PTX was done. Furthermore, in septic neonates, recruited into all previously conducted meta-analyses, exclusively one schedule of PTX administration (5 mg/kg/h for 6 hours), presented in our first randomized controlled, double-blind study, and was applied, regardless of the severity of the clinical course of sepsis.

Recently, the results of several experimental and clinical studies were published, providing evidence for neuroprotective effects of PTX. Haggar and coauthors demonstrated that twelve weeks of PTX administration in a dose of 800 mg/day caused a significant increase in blood concentration of the brain derived neutrophic factor (BNDF), in adult patients with major depressive disorder (MDD), showing clinically and statistically significant antidepressant effects compared to placebo [10]. It is also known that MDD is associated with inflammatory processes and increased concentration of IL-6 in the brain. On the other hand, BNDF is crucial for the development of the peripheral and central nervous system. It was found in the experimental studies that PTX may stimulate process of neurogenesis and prevent neuronal degeneration, especially in the hippocampus. Primarily, the increase in cAMP as well as the reduction of proinflammatory cytokines concentrations, likely played an important role in promoting neurogenesis by PTX [11]. Moreover, Zheng and coauthors [12], on the grounds of results obtained in the experimental study, suggested an important role of PTX in modulation of microglia-associated phagocytosis and the protective effects against white matter injury observed after episodes of hypoxia. It is also known that markedly increased proinflammatory cytokines concentrations due to sepsis may impair pre-oligodendrocytes, which finally causes white matter injury and impairs myelinization [13, 14]. Furthermore, recently Ruiz-Perera and coauthors, making use of a model of human neuronal stem cells, showed that PTX shifted stem cell differentiation to oligodendroglial cells. Whether it might improve the impaired process of myelination should be elucidated in experimental and clinical research. Moreover, it was also found that PTX adjuvant to risperidone alleviated negative symptoms in patients with schizophrenia and no remarkable side effects were observed. These effects could be attributed to inhibition of phosphodiesterases (PDEs) and a reduction in concentrations of inflammatory cytokines in the brain. The role of inflammation in the pathomechanism of schizophrenia is also suggested.

The results of publications quoted above present different kinds of beneficial, anti-inflammatory effects of PTX and confirm the permeability of the blood-brain barrier for this drug.

The administration of PTX as an adjunct to antibiotic therapy of sepsis, dates in our neonatal department to 1999, when we published the results of the first prospective, randomized double-blind, placebo-controlled study on the effectiveness and safety of PTX in the treatment of neonatal sepsis [15]. We found that PTX significantly decreased serum concentrations of TNF-α and IL-6 as well as reduced the mortality rate in premature infants with late-onset sepsis (LOS) caused by Gram- negative bacteria. The dosage and schedule for drug administration applied in this study attenuated the severity of the clinical course of sepsis in the group of patients treated with PTX. However, on the ground of our first results, we were not able to make an unambiguous conclusion about the best dosage and schedule of drug administration, because it was the first clinical research project with PTX in preterm infants with sepsis. During subsequent several years of clinical observation, after collecting data and experience, we made several modifications and established different schedules for PTX administration in septic neonates. They are based principally on the clinical symptoms and the values of IL-6 serum concentrations found during sepsis. These parameters indicate the necessity for the modification of dosages and the length of drug administration. It is widely accepted that IL-6 serum concentration is a good and early marker of neonatal sepsis. This cytokine is released within 2 hours after onset of bacteremia, peaks at approximately 6 hours and usually declines over the following 24 hours

[16]. However, IL-6 serum concentration may fluctuate at the beginning of therapy within 3-4 days. Moreover, IL-6 serum concentrations might be significantly elevated, even up to 48 hours, prior to the onset of clinical sepsis [17]. Although some investigators have found that neonatal IL-6 response is comparable to that found in adults while others have reported diminished IL-6 production, we occasionally observed extremely high IL-6 serum concentrations, even excessive values of 100.000 pg/ml. (normal value <40 pg/ml). The highest value of IL-6 serum concentration found in preterm neonates with early onset sepsis (EOS), hospitalized in our unit, reached 450.000 pg/ml. In these cases, when we observed IL- 6 serum concentrations above 50.000 pg/ml a standard dose of PTX (5mg/kg/hour, given for 6 hours) caused only minimal and transient effect on both IL-6 serum concentration and perfusion disturbances. After doubling the dosage of PTX (10 mg/kg/hour) and extending the period of drug administration (24 hours infusion given during two consecutive days), we obtained both a significant decrease in IL-6 serum concentration and capillary refill time reduction. A recent analysis of 480 episodes of LOS diagnosed in 208 preterm neonates born below 32 weeks of gestational age showed that increased IL-6 serum concentrations were associated with sepsis severity and mortality risk [18]. We confirm that correlation and suggest that IL-6 serum concentration might serve as a prognostic parameter for severity as well as mortality risk in neonatal sepsis. On the basis of our clinical experience, we also confirm that rapid intervention with intravenous PTX as an adjunct of antibiotic therapy in suspected neonatal sepsis, diminishes the risk of perfusion disturbances, alleviates metabolic acidosis, and treats them successfully. The duration of PTX infusion and the dosage of drug-infused should be differentiated according to the following clinical conditions: metabolic acidosis, perfusion and coagulation disorders, the necessity to use non-invasive or invasive ventilatory support, the appearance of thrombotic necrosis on the skin surface and the magnitude of the values of IL-6 serum concentrations. As for the number of total days of drug administration, we suggest the continuation of therapy with PTX as long as the antibiotics are supplied. However, during the treatment, the dosages of PTX may be reduced or increased, according to the clinical conditions and the observed values of IL-6 serum concentrations.

Below we propose four different schedules of PTX administration in therapy of neonatal sepsis. The proposal is based on clinical experiences and retrospectively analyzed data found in a group of approximately 800 premature septic patients with confirmed sepsis of different degrees of severity. We would like to emphasize that all adjustments of dosages and the length of PTX administration were performed according to clinical conditions and IL-6 serum concentrations after parental consent was obtained.

Sepsis without perfusion disorders: clinical symptoms of sepsis with increased serum concentrations of IL-6, (blood culture positive or negative) – no perfusion disorders, no metabolic acidosis: PTX administered in a dose of 5 mg/kg/h and infused for 6 hrs a day. (in case of feeding intolerance – the possibility of reducing a dose to 2.5 mg/kg/h)

Sepsis with perfusion disorders: prolonged capillary refill time (CRT >3 sec.), increased lactate concentration, metabolic acidosis, significantly increased concentration of inflammatory markers: IL-6, CRP, PCT: PTX administered in a dose of 5 mg/kg/h and infused for 12 or 24 hrs a day.

Septic shock: start infusion of PTX about 1-2 hours after the previous beginning of the administration of fluids and catecholamines and/or hydrocortisone. PTX is administered in a dose of 5mg/kg/h and continued for 24 hrs.

Significantly increased serum IL-6 concentrations >50.000 pg/ml: visible thrombotic skin necrosis: PTX in a dose of 10 mg/kg/h infused for 12-24 hrs and continued usually within 1 to 2 days then switch to administration with a dose of 5 mg/kg/h infused for 12-24 hrs.

In 2016, based on retrospective analysis, we published the results of sepsis therapy diagnosed in very low birth weight infants [19]. Among the 458 infants with confirmed sepsis (median birthweight 1010.0 g; median gestational age: 29 weeks), death occurred in 19 of those infants (4.2%). In comparison to data presented by others, our results seemed to be promising. We declare that PTX, as an adjunct to antibiotic therapy of confirmed or suspected sepsis in preterm neonates, has been used in our department continuously since 1999. However,

the dosage and schedule of PTX administration have been adjusted to clinical symptoms and the values of IL-6 serum concentration, which markedly improved the results of treatment.

Declarations

Suggestion: based on our own clinical experiences and data from experimental and clinical studies presented above, we suggest the possible, beneficial effects of PTX when given as an adjunct therapy to antibiotics in neonatal sepsis. It seems to be an important part of treatment, especially when markedly increased inflammatory response is observed, and perfusion is significantly disturbed. An adjunct to antibiotics, therapy with PTX alleviates the clinical course of sepsis and it might limit the risk of abnormalities of brain development in premature infants. However, we realize that our suggestion is mostly based on clinical observations and retrospective analysis, and therefore it should be treated as a consultative opinion.

Author Contribution: The authors contributed to the article and approved the submitted version.

Conflict of interest: The authors declare no commercial or financial relationships that could be construed as a potential conflict of interest**.**

References

1. Martin CR. “Chapter: Infection Disease and Immunology: in Year Book of Neonatal and Perinatal Medicine.” *Elsevier, Inc* 94 (2016).
2. Hagberg, Henrik, Carina Mallard, Donna M. Ferriero, and Susan J. Vannucci, et al. “The role of inflammation in perinatal brain injury.” *Nat Rev Neurol* 11 (2015): 192-208.
3. Chau, Vann, Rollin Brant, Kenneth J. Poskitt, and Emily WY Tam, et al. “Postnatal infection is associated with widespread abnormalities of brain development in premature newborns.” *Pediatr Res* 71 (2012): 274-279.
4. Cappelletti, Monica, Silvia Della Bella, Enrico Ferrazzi, and Domenico Mavilio, et al. “Inflammation and preterm birth.” *J Leukoc Biol* 99 (2016): 67-78.
5. Giordano, Vito, Sophie Stummer, Claudia Lindtner, and Renate Fuiko, et al. “Neonatal sepsis is associated with behavioral abnormalities in very low birthweight infants at preschool age.” *Front Pediatr* 10 (2022): 906379.
6. Rees, Clare M., Agostino Pierro, and Simon Eaton. “Neurodevelopmental outcomes of neonates with medically and surgically treated necrotizing enterocolitis.” *Arch Dis Child Fetal Neonatal Ed* (2006).
7. Dong, Jianqing, Xinmei Yuan, and Weiwei Xie. “Pentoxifylline exerts anti-inflammatory effects on cerebral ischemia reperfusion-induced injury in a rat model via the p38 mitogen-activated protein kinase signaling pathway.” *Mol Med Rep* 17 (2018): 1141-1147.
8. Harris, Emma, Sven M. Schulzke, and Sanjay K. Patole. “Pentoxifylline in preterm neonates: a systematic review.” *Paediatr Drugs* 12 (2010): 301-311.
9. Pammi, Mohan, and Khalid N. Haque. “Pentoxifylline for treatment of sepsis and necrotising enterocolitis in neonates.” *Cochrane Database Syst Rev* 6 (2023).
10. El-Haggar, Sahar Mohamed, Mai AbdelRaouf Eissa, Tarek Mohammed Mostafa, and Khaled Sabry El-Attar, et al. “The phosphodiesterase inhibitor pentoxifylline as a novel adjunct to antidepressants in major depressive disorder patients: a proof-of-concept, randomized, double-blind, placebo-controlled trial.” *Psychother Psychosom* 87 (2018): 331-339.
11. Siegel, Ashley N., Nelson Rodrigues, Flora Nasri, and Linas Wilkialis, et al. “Novel therapeutic targets in mood disorders: Pentoxifylline (PTX) as a candidate treatment.” *Prog Neuropsychopharmacol Biol Psychiatry* 104 (2021): 110032.
12. Zheng, Lili, Junqiu Jia, Yan Chen, and Renyuan Liu, et al. “Pentoxifylline alleviates ischemic white matter

injury through up-regulating Mertk-mediated myelin clearance." *J Neuroinflammation* 19 (2022): 1-15.

13. Moschopoulos, Chariton, Panagiotis Kratimenos, Ioannis Koutroulis, and Bhairav V. Shah, et al. "The neurodevelopmental perspective of surgical necrotizing enterocolitis: the role of the gut-brain axis." *Mediators of Inflammation* 2018 (2018).

14. Gamage, Teena KJB, and Mhoyra Fraser. "The role of extracellular vesicles in the developing brain: current perspective and promising source of biomarkers and therapy for perinatal brain injury." *Front Neurosci* 15 (2021): 744840.

15. Lauterbach, Ryszard, Dorota Pawlik, Danuta Kowalczyk, and Wieslaw Ksycinski, et al. "Effect of the immunomodulating agent, pentoxifylline, in the treatment of sepsis in prematurely delivered infants: a placebo-controlled, double-blind trial." *Crit Care Med* 27 (1999): 807-814.

16. Gilfillan, Margaret, and Vineet Bhandari. "Biomarkers for the diagnosis of neonatal sepsis and necrotizing enterocolitis: Clinical practice guidelines." *Early Hum Dev* 105 (2017): 25-33.

17. Küster, Helmut, Michael Weiss, Andreas E. Willeitner, and Stefanie Detlefsen, et al. "Interleukin-1 receptor antagonist and interleukin-6 for early diagnosis of neonatal sepsis 2 days before clinical manifestation." *The Lancet* 352 (1998): 1271-1277.

18. Kurul, Şerife, Sinno HP Simons, Christian RB Ramakers, and Yolanda B. De Rijke, et al. "Association of inflammatory biomarkers with subsequent clinical course in suspected late onset sepsis in preterm neonates." *Critical Care* 25 (2021): 1-10.

19. Lauterbach, Ryszard, Barbara Wilk, Agata Bochenska, and Joanna Hurkala, et al. "Nonactivated protein C in the treatment of neonatal sepsis: a retrospective analysis of outcome." *J Pediatr Infect Dis* 35 (2016): 967-971.

Citation: Lauterbach, Ryszard, and Dorota Pawlik. "May Pentoxifylline Protect Immature Brain Against Disorders Induced By Inflammatory Response In Neonatal Sepsis?." *J Neonatol Pediat Care* (2023): 101. DOI: 10.59462/JNPC.1.1.101.