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# Effect of Pentoxifylline on Late-onset Sepsis and Protein C Level in Preterm Neonates: a Double-blinded Randomized Controlled Trial

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## ABSTRACT

**Background:** Pathological coagulation system activation is linked to neonatal sepsis, which leads to disseminated intravascular coagulation. Late-onset sepsis (LOS) in preterm neonates leads to serious morbidities and increased mortality.
**Aim and objectives:** The purpose of this research was to assess how pentoxifylline affectes protein C in septic preterm infants as well as their clinical development and outcomes.
**Patients and methods:** Eighty preterm newborns who were hospitalized in Kasr Alaini, Cairo University Hospital's neonatal critical care units and with clinical or blood culture-proven LOS participated in this double-blinded, randomized controlled experiment. The pentoxifylline group got pentoxifylline (5 mg/kg/hour for six hours), whereas the control group received normal saline as a placebo. Both infusions were administrated for six successive days. Protein C levels were measured before and after the intervention.
**Result:** Gram-negative sepsis was predominant with *Klebsiella pneumonia* being the most common isolated organism. After the intervention, there was a significant increase in protein C levels in the pentoxifylline group (P value = 0.020). Significant reductions in the duration of antimicrobial therapy,duration of hospital stay in survivors and continuous positive airway pressure therapy, (P values =**0.001**, **0.012** and 0.03 respectively) were documented, as well as the decreased requirement for plasma transfusions (P value = 0.03).
**Conclusion:** In preterm newborns with LOS, pentoxifylline has a good impact on the protein C system and lengths of antibiotic treatment, hospital stay and continuous positive airway pressure therapy.
**Keywords:** Coagulation; Neonate; Pentoxifylline; Protein C; Sepsis.

## INTRODUCTION

The leading cause of newborn fatalities, particularly in middle- and low-income nations, is neonatal sepsis [(1)].

It typically occurs in conjunction with platelet fatigue, pathological activation of the coagulation system, and fibrinolytic agents. In addition, antithrombin III, protein C, and protein S levels are significantly decreased in septic neonates [(2,3)], which promotes the growth of numerous microvascular thrombi and the development of disseminated intravascular coagulation (DIC) and multiple organ failure.

Pro-inflammatory cytokines have been given the primary responsibility for the pathophysiology of sepsis because they cause DIC to form via the tissue factor-dependent route of coagulation [(4)]. Endotoxins stimulate neutrophils, macrophages, and the secretion of cytokines such as tumor necrosis factor (TNF) and interleukins as well as humoral and cellular defense systems [(5)]. Agents that control inflammation may improve outcomes since newborn sepsis mortality and morbidity are still high despite the use of strong antimicrobials.

Pentoxifylline is a non-steroidal immunomodulating drug with distinctive hemorrhagic effects that has been utilized in a variety of infectious, vascular, and inflammatory disorders in both children and adults [(6,7)]. It is a xanthine or theobromine derivative and a phosphodiesterase inhibitor. Pentoxifylline's special characteristics explain why it may be beneficial for a variety of disorders in neonates that are characterized by inflammatory cytokine cascade activation, free radical toxicity, and poor microcirculation [(8)]. Additionally, it improves platelet function by increasing erythrocyte flexibility, fibrinolytic and tissue plasminogen activator activity, and inhibiting platelet adhesion [(9)]. Additionally, it reduces blood viscosity and enhances tissue perfusion and microcirculation [(10)].

Pentoxifylline's impact on cyclic adenosine monophosphate has been linked to a wide range of outcomes, including the preservation of protein C in sepsis. Theobromine is the least toxic of the methylxanthines and has no appreciable cardiac or bronchodilator effects at therapeutic levels [(11)]. Pentoxifylline's effectiveness in treating newborn sepsis is still unknown, and published research has shown contradictory results [(4,12–17)]. Additionally, its function in the neonatal physiological inhibitory mechanism of coagulation has not yet been researched. In order to assess the possible impact of pentoxifylline on protein C in



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septic preterms, as well as their clinical outcomes, morbidities, and mortality, the study's objective was to examine these variables.

## METHODS

### Subjects

80 preterm neonates hospitalized in the neonatal critical care units at Kasr Alaini, Cairo University Hospital, with clinically diagnosed or blood culture-proven late-onset sepsis (LOS) (sepsis detected after the first 72 hours of life) participated in this double-blinded randomized controlled experiment.

### Ethical consent

**Cairo University Faculty of Medicine Research Ethics Committee authorized the project (registration number: N-30-2017). All the gurdians of the participants signed informed consent forms. We adhered to the Helsinki Declaration, the ethical guideline of the World Health Organization for human trials.**

### Inclusion criteria

Infants had at least two, or more clinical manifestations suggestive of sepsis e.g., temperature instability, cardiovascular, respiratory, neurological, or gastrointestinal manifestations, or poor reflexes in addition to one or more laboratory abnormalities suggestive of sepsis e.g., increased or decreased leucocytic count, increased immature to total neutrophil ratio or raised CRP. While exclusion criteria included neonates having major congenital malformations, grade three or four intraventricular hemorrhage, inborn errors of metabolism, congenital infections, hypoxic-ischemic encephalopathy or had developed necrotizing enterocolitis before intervention. Also, patients receiving steroids, other phosphodiesterase inhibitors (milrinone, caffeine citrate, sildenafil, or theophylline), or drugs of known interactions with pentoxifylline (anticoagulants or antiplatelet aggregation) were not enrolled.

### Intervention

The identical vials of pentoxifylline and placebo were coded using computer-generated random numbers and were issued according to trial number. The representative nurse practitioner assigned to medication preparation had the code. Pentoxifylline or 0.9 percent sodium chloride solution as placebo were randomly assigned to all patients with suspected or culture-proven LOS. The pentoxifylline group (n=40) was administered a daily dosage of 5 mg/kg/hour for 6 hours over the course of 6 days in a row [(18)] (Trentoximal 100 mg/5 ml, Alex Co. for Egy pharma, Egypt). The amount of pentoxifylline needed each day was taken out of the ampoule and diluted up to 12 ml with normal saline.

The infusion rate was set at 2 mL/hour using a controlled-volume infusion pump, whereas the placebo group (n=40) received 12 mL of normal saline over a period of 6 hours each day for 6 consecutive days. In identical syringes, pentoxifylline (an invisible solution equivalent to a placebo) and saline were administered. The laboratory staff, residents, and nurses who record daily notes and vital signs were blinded to the intervention. Similar amounts of the medication or sodium chloride solution (0.9%) were administered.

### Outcomes

The main results were the protein C level before and after the pentoxifylline or placebo treatment course, the impact of intravenous pentoxifylline as an adjunct to antibiotic therapy on the clinical condition, hematological abnormalities, and mortality in neonates with suspected or confirmed sepsis. The secondary outcomes included impacts on how long septic newborns needed to remain in the hospital, the kind and duration of ventilator support, and the emergence of necrotizing enterocolitis, chronic lung disease, intraventricular hemorrhage, or retinopathy of prematurity.

### Clinical and Laboratory Workup

Before and throughout the course of therapy, a thorough clinical examination was conducted. Throughout the course of the intervention, daily measurements of blood pressure, capillary refill time, heart rate, and urine output were taken. Complete blood count, total white blood cells with a differential count by CELL-DYN Ruby hematology analyzer, Abbott, U.S.A. prothrombin time (PT), and activated partial thromboplastin time (APTT) by Stago STA Compact coagulation analyzer, Diagnostica Stago Inc, France were all part of the laboratory workup. These tests were also performed before the patient started taking the medication, every other day during the course of the drug infusion, and at the end of the infusion, or whenever clinically indicated.

In addition, liver, and kidney function tests, and D dimer (in cases suspected to have DIC) were assessed by ZYMUTEST DDimer ELISA kit, Hyphen Biomed, France, and blood culture or any other needed cultures (with samples obtained before the start of antibiotic therapy) were conducted. Blood specimens for culture were never obtained from the catheters. Protein C levels were assessed before and after the treatment course using an Enzyme-Linked Immunosorbent Assay technique Human Protein C (P-C) ELISA Kit Hanghai Korain Biotech CO., LTD. Shanghai, China.

### Test principle

This kit used enzyme-linked immune sorbent assay (ELISA) based on the Biotin double antibody

sandwich technology to assay the Human Protein C (P-C) Protein C Added (P-C) to the wells, which are pre-coated with Protein C(P-C) monoclonal antibody and then was incubated. After that, anti-P-C antibodies were labeled with biotin and added to unite with streptavidin-HRP, which formed immune complexes. Unbound enzymes were removed after incubation and washing. Substrates A and B were added. The solution turned to blue and changed into yellow with the effect of acid. The shades of solution and the concentration of Human Protein C (P-C) are positively correlated.

**Sample used**

The serum was allowed to clot for 10-20 minutes at room temperature and centrifuged at 2000-3000 RPM for 20 minutes. The supernatants were collected carefully. Assay range was：0.1 mg/L→45 mg/L and the sensitivity: 0.06 mg/L. Each 40 μg/ml equaled 160 U/dl. Cranial ultrasound and chest or abdominal X-rays were done routinely or when clinically indicated. Fundus examination before discharge was done for survivors.

**Management of Sepsis and Complications**

Both groups received the same standard medical treatment for sepsis, which included first-line antibiotics such as gentamicin and ampicillin/sulbactam. Following the discovery of blood culture findings, antibiotics were modified in accordance with the discovered bacteria's susceptibility. Treatment was switched to the second line of antibiotics when the clinical situation became worse while it was being administered, and this continued until the cultures' findings came back positive or the condition got better.

Mechanical breathing, volume resuscitation (crystalloid and colloid solutions), and/or vasopressors such as dopamine, dobutamine, and norepinephrine were administered to patients with shock; this was the same for both groups. Infants were further given treatment for DIC as appropriate, including fresh frozen plasma (FFP), vitamin K, platelets, and/or packed red blood cell transfusions.

***Statistical Analysis***

A prospective power analysis was performed using MedCalc software version 15.8 to establish the ideal sample size. According to earlier findings from the investigation of blood protein C levels in pentoxifylline-treated septic patients [(19)], a minimum sample size of 20 patients was required for each group in order to achieve the power of 0.8 and an alpha error of 0.05. Version 17 of the Statistical Package for the Social Sciences (SPSS) was used for the statistical analysis. Categorical data were summarized using descriptive statistics, such as frequencies and percentages, whereas continuous variables were done so using means, medians, standard deviations, and interquartile ranges.

The skewness and kurtosis tests were used to determine if continuous variables had a normal distribution. Categorical data were subjected to the $chi^2$ test (or Fisher's exact test, if applicable), while continuous variables with normally distributed data were subjected to the Student's t-test and non-normally distributed data were subjected to the Mann-Whitney test. P-values less than 0.05 were regarded as significant.

**RESULTS**

**Patients' Characteristics**

Eighty neonates who met our eligibility requirements were included. As can be seen in table 1, there were no significant changes in the baseline characteristics of the neonates in the two groups with respect to age, gender, gestational age, birth weight, Apgar score, and delivery method. Gram-negative sepsis predominated, with Klebsiella pneumonia being the most frequently isolated pathogen. In terms of culture-proven sepsis, 12 patients in the pentoxifylline group and 15 patients in the placebo group had the condition (41.6 percent and 46.6 respectively). There were no statistically significant variations between the isolated organisms in either group (Table 1).

**Table 1. Patients' characteristics of the two groups**

| Parameters | Pentoxifylline group (n=40) | | | Placebo group (n=40) | | | P-value |
|---|---|---|---|---|---|---|---|
| **Age on Admission (days)** | **Median** | **1st quartile** | **3rd quartile** | **Median** | **1st quartile** | **3rd quartile** | 0.873 |
| | 5.00 | 4.00 | 6.00 | 5.00 | 4.00 | 6.00 | |
| **Gestational Age (weeks)** | 32.2 ± 2.4 | | | 32 ± 2.5 | | | 0.82 |
| **One minute-APGAR** | 5.76 ± 1.1 | | | 5.71 ± 1.1 | | | 0.86 |
| **Five minute-APGAR** | 8.1 ± 0.7 | | | 8.1 ± 0.7 | | | 1 |
| **Birth weight (gm)** | 1640 ± 380 | | | 1610 ± 390 | | | 0.71 |
| **Gender, male (%)** | 21 (52.5%) | | | 22 (55%) | | | 0.82 |
| **Gender, female (%)** | 19 (47.5%) | | | 18 (45%) | | | |
| **Mode of Delivery** | | | | | | | |
| ***Vaginal (%)*** | 13 (32.5%) | | | 15 (37.5%) | | | 0.64 |
| ***Cesarean Section (%)*** | 27(67.5%) | | | 25(62.5%) | | | |
| **Clinical Manifestations on Admission** | | | | | | | |
| ***Poor suckling*** | 40(100%) | | | 39(97.5%) | | | 1 |
| ***Absent Moro reflex*** | 40(100%) | | | 39(97.5%) | | | 1 |
| ***Hypotension*** | 16(40%) | | | 16(40%) | | | 1 |
| ***Bradycardia*** | 9(22.5%) | | | 7(17.5%) | | | 0.58 |
| ***Apnea*** | 9(22.5%) | | | 8(20%) | | | 0.78 |
| ***Respiratory distress*** | 22(55%) | | | 19(47.5%) | | | 0.50 |
| ***Vomiting*** | 15(37.5%) | | | 16(40%) | | | 0.82 |
| ***Gastric residual*** | 26(65%) | | | 26(65%) | | | 1 |
| ***Abdominal distension*** | 25(62.5%) | | | 26(65%) | | | 0.82 |
| ***Hypothermia*** | 15(37.5%) | | | 15(37.5%) | | | 1 |
| ***Hyperthermia*** | 8(20%) | | | 7(17.5%) | | | 0.77 |
| **Positive blood culture (%)** | 12 (30%) | | | 15 (37.5%) | | | 0.48 |
| **Isolated microorganisms** | | | | | | | |
| ***Gram positive organisms (%)*** | 4 (33%) | | | 5 (33%) | | | 1 |
| **CONS** | 3(25%) | | | 4(26.6%) | | | 1 |
| **Staphylococcus aureus(MRSA)** | 1(8.3%) | | | 0(0%) | | | 1 |
| **GBS** | 0(0%) | | | 1(6.6%) | | | 1 |
| **Gram-negative organisms (%)** | 8 (66.6%) | | | 10 (66.6%) | | | 0.59 |
| ***Klebsiella pneumonia*** | 5(41.6%) | | | 7(46.6%) | | | 0.53 |
| ***Acinetobacter spp.*** | 1(8.3%) | | | 2(13.3%) | | | 1 |
| ***Escherichia coli*** | 1(8.3%) | | | 1(6.6%) | | | 1 |
| ***Pseudomonas aeroginosa*** | 1(8.3%) | | | 0(0%) | | | 1 |

*Abbreviations; CONS = Coagulase Negative Staphylococcus, GBS = Group B Streptococcus, MRSA = Methicillin Resistant Staphylococcus.*

**Outcomes and Adverse Effects**

Table 2 shows that the level of protein C did not differ between both groups before the administration of pentoxifylline. However, it was significantly higher in the pentoxifylline group after its administration. Table 3 demonstrated that the pentoxifylline group had insignificantly higher platelet count, lower CRP, lower PT, PTT, and higher hemoglobin levels than the placebo group after intervention.

**Table 2. Protein C levels before and after intervention**

| | Pentoxifylline group (PTX) (n=40) | Control group (n=40) | **P-value** |
|---|---|---|---|
| Protein C before intervention mg/L | 2.8 (0.84-13.9) | 3.1(0.5-13.7) | 0.88 |
| Protein C after intervention (mg/L) | 6.2 (0.99-12.6) | 3.5(1.8-11.6) | **0.020*** |

* = Significant

**Table 3. Hematological parameters in the study groups before and after intervention**

*ANC = Absolute Neutrophilic Count, aPTT = activated partial thromboplastin time, CRP = C-reactive protein, INR = international normalization ratio, IT Ratio = immature neutrophils/total neutrophils ratio, PT=prothrombin time.*

| **Before intervention** | | | | **After intervention** | | |
|---|---|---|---|---|---|---|
| | **Pentoxyphylline group (n=40)** | **Placebo group (n=40)** | **P value** | **Pentoxyphylline group (n=40)** | **Placebo group (n=40)** | **P value** |
| **White blood cell countX $10^9$/L** | 9.2(1.7-39) | 7.6(1.9-39) | 0.73 | 13(4.1-30) | 12.5(3.9-23) | 0.83 |
| **ANC X $10^9$/L** | 3.5(0.78-21.3) | 3.8(0.9-22.2) | 0.97 | 7.3(2-13) | 6.5(1.3-13) | 0.35 |
| **IT ratio** | 0.2(0-0.4) | 0.4(0-0.23) | 0.55 | 0.4(0-0.23) | 0.05(0-0.23) | 0.48 |
| **Immature neutrophils (%)** | 14.5(0-40) | 14(0-30) | 0.76 | 3(0-19) | 3(0-15) | 0.98 |
| **CRP (mg/dl)** | 24(12-96) | 48(12-96) | 0.94 | 6(0-48) | 12(0-96) | 0.63 |
| **Hemoglobin (g/dl)** | 15(9.1-18.3) | 14.7(9-18) | 0.78 | 12.7(7.1-15) | 12(9-15) | 0.98 |
| **Platelets X $10^9$/L** | 170(44-327) | 170(45-330) | 1 | 191(27-461) | 180(12-461) | 0.84 |
| **PT (sec)** | 20(13-28) | 20(13-28) | 1 | 14(11-22) | 14.9(11-26) | 0.89 |
| **INR** | 1.7(1-2.5) | 1.7(1-2.5) | 1 | 1.1(1-2) | 1.2(1-2.3) | 0.98 |
| **aPTT (sec)** | 56(37-82) | 55(37-82) | 0.98 | 45(35-85) | 45(35-86) | 1 |

There was no significant difference between both groups before and after intervension as regard AST, ALT, creatinine and each of total and direct bilirubin (Table 4).

**Table 4. Liver and kidney functions of study groups before and after intervention**

| **Before intervention** | | | | **After intervention** | | |
|---|---|---|---|---|---|---|
| **Value** | **Pentoxyphylline group (n=40)** | **Placebo group (n=40)** | **P value** | **Pentoxyphylline group(n=40)** | **Placebo group (n=40)** | **P value** |
| **AST (u/l)** | 45(13-345) | 45(13-345) | 1 | 35(13-304) | 37(13-258) | 0.85 |
| **ALT (u/l)** | 15(5-146) | 16 (5-156) | 0.88 | 13(5-270) | 13(7-157) | 0.98 |
| **Creatinine (mg/l)** | 0.8(0.2-2.7) | 0.8 (0.1-2.3) | 0.98 | 0.35(0.01-2) | 0.3(0.01-2.1) | 0.9 |
| **Bilirubim (total) (mg/dl)** | 5.5(2-14) | 6.5 (2-17) | 0.56 | 4(1.2-11) | 4(2-12) | 1 |
| **Bilirubin (direct) (mg/dl)** | 0.2(0.1-0.7) | 0.2 (0.1-0.8) | 1 | 0.2(0.1-1.3) | 0.2(1-1.3) | 1 |

*ALT = Alanine Transaminase, AST = Aspartate Transaminase.*

Additionally, thrombocytopenia, bleeding tendency, and metabolic acidosis did not show any difference between the two groups before intervention (Table 5) while metabolic acidosis, hepatic failure, oliguria/anuria, DIC, development of shock, bleeding tendency, and MODS were less frequent in the pentoxifylline group after six days of treatment but without statistical significance. Despite this, the pentoxifylline group saw considerably fewer FFP transfusions. Duration of NICU stay in survivors, antimicrobial therapy and continuous positive airway pressure (CPAP) treatment were all statistically significantly shorter in the pentoxifylline group. The length of intermittent obligatory breathing, high-frequency oscillatory ventilation, total time spent on respiratory support, various short-term morbidities, and survival rates were all shown to be non-statistically different between the two groups (Table 6).

**Table 5: The incidence of organ dysfunction before and after the course of 6 days therapy**

| Value | Pentoxyphylline group (n=40) | Control group (n=40) | P- value |
|---|---|---|---|
| **Thrombocytopenia (before intervention)** | 13 (33%) | 14 (34%) | 0.81 |
| **Thrombocytopenia (after intervention)** | 12 (33%) | 16 (42%) | 0.35 |
| **Bleeding tendency(before intervention)** | 19(49%) | 21 (51%) | 0.65 |
| **Bleeding tendency (after intervention)** | 8 (22%) | 9 (23%) | 0.78 |
| **Metabolic acidosis (before intervention)** | 21 (53% | 19 (49%) | 0.65 |
| **Metabolic acidosis(after intervention)** | 7 (18%) | 10 (24%) | 0.41 |
| **Hepatic failure** | 3 (8%) | 5 (12%) | 0.71 |
| **Oliguria/Anuria** | 5 (13%) | 11 (27%) | 0.09 |
| **DIC** | 4 (10%) | 5 (12%) | 1 |
| **Development of shock** | 2 (8%) | 8 (20%) | 0.08 |
| **MODS** | 3 (8%) | 5 (12%) | 0.71 |

*DIC= disseminated intravascular coagulopathy, MODS= multi organ dysfunction syndrome.*

**Table 6. Duration of NICU stay, different management strategies, and short-term morbidities**

| Parameters | Pentoxifylline group (n=40) | | | Placebo group (n=40) | | | P-value |
|---|---|---|---|---|---|---|---|
| **Duration of NICU stay (days)** | **Median** | **1st quartile** | **3rd quartile** | **Median** | **1st quartile** | **3rd quartile** | **0.012*** |
| | 11.00 | 10.00 | 20.00 | 15.00 | 12.00 | 25.00 | |
| **Duration of antimicrobial therapy (days)** | 8.00 | 7.00 | 14.00 | 13.00 | 10.00 | 21.00 | **0.001*** |
| **Duration of CPAP (days)** | 4(0-15) | | | 5(0-20) | | | **0.03 *** |
| **Duration of IMV (days)** | 0(0-20) | | | 1(0-20) | | | 0.98 |
| **Duration of HFOV (days)** | 0(0-5) | | | 0(0-5) | | | 1 |
| **Bleeding tendency** | 19(47.5%) | | | 21(52.5%) | | | 0.65 |
| **Total duration of respiratory support (days)** | 5(0-35) | | | 7.5(3-40) | | | 0.06 |
| **Number of FFP transfusions** | 1 (0-2) | | | 5 (0-5) | | | **0.03*** |
| **CLD** | 2 (l5%) | | | 4 (9%) | | | 0.68 |
| **NEC** | 3 (8%) | | | 4 (10%) | | | 1 |
| **Severe IVH** | 2 (7%) | | | 3 (9%) | | | 1 |
| **ROP** | 3 (19%) | | | 5 (27%) | | | 0.71 |
| **Survival** | 34 (85%) | | | 33 (81%) | | | 0.76 |
| **Hepatic failure** | 3 (8%) | | | 5 (12%) | | | 0.71 |
| **Oliguria/anuria** | 5 (13%) | | | 11 (27%) | | | 0.09 |
| **DIC** | 4 (10%) | | | 5 (12%) | | | 1 |
| **Development of shock** | 2 (8%) | | | 8 (20%) | | | 0.09 |
| **MODS** | 3 (8%) | | | 5 (12%) | | | 0.71 |

*CLD = Chronic lung disease, CPAP = Continuous positive airway pressure, HFOV = High-frequency oscillatory ventilation, IMV = Intermittent mandatory ventilation, IVH = Intraventricular haemorrhage, MODS = Multiple organ dysfunction syndrome, NICU = Neonatal intensive care unit, NEC = Necrotizing Enterocolitis , ROP =Retinopathy of prematurity* * = Significant

## DISCUSSION

With a frequency of 6.5–38 per 1000 live births, neonatal sepsis is recognized as the leading cause of infant mortality [20,21]. Sepsis may cause significant morbidity and death at rates of up to 10%–20% for all babies and 20%–30% for infants with extremely low birth weights [22]. Ineffective medications against multidrug-resistant bacteria or weakened host defense systems in preterm newborns may be to blame for the morbidity and death [23,24]. To improve the effectiveness of antimicrobial medicines and combat an excessive or uncontrolled inflammatory response in sepsis, adjuvant treatments may become more and more crucial [25,26].

In an effort to find a new adjuvant therapy to antimicrobial therapy for the treatment of neonatal sepsis to prevent the complications of activation of inflammatory cytokines that activate the coagulation system and inhibit both fibrinolyses, and decrease levels of natural anticoagulant factors [27], we documented that pentoxifylline therapy has a significant beneficial effect on the protein C system. This is in line with the findings of **Boldt *et al.***, who reported that continuous intravenous administration of pentoxifylline for five days beneficially increased concentrations of protein C in pentoxifylline-treated sepsis and trauma patients [19]. This is attributed to the anti-inflammatory response of pentoxifylline by decreasing tumor necrosis factor [TNF] α in the pentoxifylline treated group, which is an inflammatory cytokine that activates the coagulation system that results in the consumption of natural anticoagulants [7].

It is noteworthy as well that we documented a lower frequency of FPP in the pentoxifylline-treated group, this is akin to the findings by **Adel and co-workers** [4] who reported a much lower need for plasma transfusion in the pentoxifylline group despite having a more rapid correction of coagulation abnormalities in the placebo group which was attributed to the more regular transfusions of FFP.

As for thrombocytopenia in the pentoxifylline group, the percentage was the same before and after intervention (33%). Yet, in the placebo group, it was 34% before the intervention and became 42% after the intervention. In the study by **Adel *et al.,*** [4] the pentoxifylline group had a statistically significantly higher platelet count than the placebo group while another report disclosed a statistically significantly lower incidence of thrombocytopenia in the pentoxifylline group [7]. Our study demonstrated a lower incidence of metabolic acidosis, oliguria/anuria, DIC, hepatic dysfunction, renal insufficiency, and MODS after intervention in the pentoxifylline group though these differences were not statistically significant. **Akdag *et al.,*** [17] demonstrated similar results. In contrast, **Adel *et al.,*** and **Shabaan *et al.,*** demonstrated a statistically significant lower incidence of these outcomes after intervention in the pentoxifylline group [4,7]. A recent meta-analysis found that pentoxifylline medication considerably lowers metabolic acidosis but has no effect on oliguria/anuria or disseminated intravascular coagulopathy [28]. Pentoxifylline did not seem to reduce mortality in preterm babies with suspected or confirmed LOS. Previous research has shown that it has little impact on preterm infant mortality, which is consistent with our results [7,13,17]. In contrast, **Lauterbach *et al.* and Ali *et al.,*** findings' [12,16] showed a significant decline in infant mortality in those taking pentoxifylline. Similar to that, a Cochrane analysis has shown that septic neonates who received pentoxifylline as an adjuvant treatment to antibiotics saw a statistically significant decrease in all-cause mortality throughout the hospital stay when compared to septic neonates who received a placebo [18]. Pentoxifylline, however, had no appreciable effect on death from newborn sepsis, according to a more recent meta-analysis that included seven randomized controlled trials (RCTs) and 439 neonates [28]. The variations across studies might be attributed to the research demographics, pentoxifylline dosage, and the etiological agents.

The pentoxifylline group had a statistically significant shorter duration of CPAP therapy and anti-microbial therapy, while both groups' durations of traditional mechanical ventilation, high-frequency oscillatory ventilation, and overall respiratory support were comparable. This was another significant finding of our study. The findings of the research by **Shabaan *et al.,*** [7] which revealed that the duration of respiratory support and that of antibiotic treatment were considerably shorter in the pentoxifylline group provide some support for these findings. Pentoxifylline's anti-inflammatory properties, together with its bronchodilator, diuretic, and respiratory muscle stimulant properties, may explain the reduction in inflammatory markers and improvement in the clinical state [29].

In the pentoxifylline group, our investigation found that the length of hospitalization was significantly shorten. This is in line with the findings of three RCTs [4,7,16] and the meta-analysis [28], which showed that the pentoxifylline group's hospital stay was much shorter. The short-term morbidities of NEC, chronic lung disease, retinopathy of prematurity, and intraventricular hemorrhage were not affected by pentoxifylline in this trial. These results are validated by earlier research [7,17,18]. A possible risk of intraventricular hemorrhage associated with premature delivery was suspected during treatment with pentoxifylline [8].

However, it is comforting to know that pentoxifylline therapy for critically sick preterm neonates with sepsis did not cause any notable side effects, such as thrombocytopenia and hemorrhage, in the earlier trials [9,18]. However, owing to its impact on platelets, red blood cells, and plasma fibrinogen levels, it is contraindicated in

individuals with recent cerebral hemorrhage[8]. In this investigation, we did not see any pentoxifylline therapeutic side effects, and this finding is consistent with the findings of the Cochrane review on pentoxifylline therapy in newborn sepsis [18].

## CONCLUSION

This double-blinded RCT showed that pentoxifylline therapy has a significant beneficial effect on the protein C system, duration of antibiotic therapy, duration of hospitalisation as well as the duration of CPAP support in preterm infants with LOS. Moreover, it improved some clinical manifestations of neonatal sepsis and was associated with fewer needs for plasma transfusions without side effects on the neonates. Further studies of its benefits are needed for a further recommendation of its routine use in septic neonates.

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