ORIGINAL ARTICLE

Pentoxifylline and Pentaglobin adjuvant therapies for neonatal nosocomial sepsis in neonates less than 1500g weight

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Abstract

Objective: To compare different support therapies in very low birth-weight preterm neonates with nosocomial sepsis.

Methods: This clinical pilot study was conducted at the Bagcilar Research and Training Hospital, Istanbul, Turkey, from September 2015 to November 2016. Preterm infants appropriately sized for a gestational age of < 32 weeks and < 1,500g were included in the study. Pentaglobin was initiated on the day of diagnosis of nosocomial sepsis to very low birth-weight preterm neonates as a support therapy in addition to antibiotics: 5 ml/kg per day of pentaglobin was infused over a four-hour period on three consecutive days. Pentoxifylline (5 mg/kg every 6 hours) was administered to premature infants with sepsis on three successive days.

Results: Of the 41 neonates, 19(46.3%) were girls and 22(53.7%) were boys. Vital signs, haematologic tables, peripheral blood smear left shift ratio, and blood-gas parameters did not differ significantly between the groups ($p>0.05$), but the C-reactive protein (mg/dl) values significantly decreased after pentoxifylline treatment ($p<0.05$). Coagulase-negative staphylococci were the most frequently isolated bacteria in the two groups (n=4; 19% vs. n=4; 20%). There was no difference in isolated microorganisms. There was no significant difference in intraventricular haemorrhage, necrotising enterocolitis, periventricular leukomalacia or symptomatic patent ductus arteriosus in the neonates when comparing the two groups and no systemic reactions were observed during adjuvant therapy in the preterm neonates ($p>0.05$). The total duration of hospitalisation was 49.46±13.52 days for the pentaglobin group and 44.21±11.1 days for the pentoxifylline group neonates.

Conclusion: Pentoxifylline treatment for nosocomial sepsis decreased C-reactive protein levels and heart rate more than pentaglobin therapy.

Keywords: Immunoglobulins, Pentoxifylline, Very low birth weight. (JPMA 67: 1482; 2017)

Introduction

Nosocomial sepsis in neonates continues to be a major cause of mortality and morbidity in neonatal intensive care units (NICUs). The major outcome of nosocomial sepsis, despite advances in neonatal care and the use of different antibiotics and adjuvant therapies, is related to a lack of sufficient improvement in the neonatal immune system and interactions between the microorganisms and neonatal responses.[1]

Nowadays, nosocomial sepsis treatment is determined by international neonatal guidelines, which recommend first-choice antibiotics regimens according to culture-proven or unproven sepsis.[1] These guidelines include known or newly supported agents for neonatal sepsis, which are used for extremely low birth-weight neonates because these neonates generally require increased instrumentation, total parenteral feeding, and delayed enteral full feeding time.

Pentaglobin (PG) is an immunoglobulin M (IgM)-enriched intravenous immunoglobulin (IVIG). IgM is 100 to 400 times greater than immunoglobulin G (IgG), and the opsonisation of bacteria by IgM is also approximately 1,000 times greater than IgG.[2] Despite Cochrane not recommending it, pentaglobin is still used as a supportive agent in the treatment of newborns with nosocomial sepsis in many newborn units. Pentoxifylline (PTX), a phosphodiesterase inhibitor, decreases tumour necrosis factor-alpha, interleukin-6 and interferon-gamma, and some studies have discussed its adjunct therapy use in the treatment of neonatal sepsis.

The present study was planned to compare different support therapies in very low birth-weight (VLBW) preterm neonates with nosocomial sepsis.

Patients and Methods

This clinical pilot study was conducted in the NICUs of Bagcilar Research and Training Hospital, Istanbul, Turkey, from September 2015 to November 2016. Preterm infants

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appropriately sized for a gestational age of < 32 weeks and < 1,500g were included in the study. Neonates with congenital (cardiac, pulmonary, or gastrointestinal) anomalies or metabolic diseases known to affect energy or nutrient metabolism were excluded. The study protocol was approved by the institutional ethical committee, and written informed consent from a parent was obtained for each child. Gestational age was calculated from maternal history or estimated using the Ballard score.

Our data collection method was included to structured observation of nosocomial sepsis and use of appropriate administrative data. Infants were randomly allocated within six hours after birth to receive PG or PTX. Eligible neonates were entered into the study based on a 1:1 adjuvant therapy allocation to the PG or PTX group. Adjuvant therapy was prepared by the hospital pharmacy and so the investigators and nursing staff were blind to treatment allocation.

We hypothesised that PG treatment of nosocomial sepsis could be used as an adjunct therapy without any adverse short-term reactions, even in VLBW preterm infants.[3] Neonates in group 1 who had nosocomial sepsis were treated with intravenous IgM-enriched IVIG-prepared PG (38 g/l IgG, 6 g/l IgM, and 6 g/l IgA; Biotest, Dreieich, Germany; 5 ml/kg per day every 4 hours for 3 consecutive days) as an adjunct therapy to a classical nosocomial sepsis antibiotic treatment protocol.

Neonates in group 2 who had nosocomial sepsis were treated with intravenous PTX (Trental® 100 mg/5 ml; Hoechst Marion Roussel, Istanbul; 5 ml/kg per day every 6 hours for 3 consecutive days) as a supportive therapy to a classical nosocomial sepsis antibiotic treatment protocol.

Nosocomial sepsis was defined in neonates who survive for 48 hours or more in the NICU without a diagnosis of neonatal sepsis at the time of admission. Proven neonatal sepsis is defined as having a positive blood culture accompanied by systemic signs of infection (respiratory distress, apnoea, abdominal distention, etc.) in the first 28 days of life. Suspected neonatal sepsis is defined as having negative blood, urine, and cerebrospinal fluid (CSF) cultures, but with no significant clinical signs of infection plus supporting laboratory parameters: an immature-to-total neutrophil ratio (I/T ratio) greater than 0.2, a total leucocyte count of either < 5 x 10^9/l or > 15 x 10^9/l, thrombocytopenia (< 150,000/mm^3), and a C-reactive protein (CRP) level above 1 mg/dl. Meningitis was diagnosed when there was a high leukocyte count (> 20/mm^3), a high protein concentration (> 150 mg/dl) in the CSF, and bacterial growth in a CSF culture.[4-7]

The blood culture results were evaluated after the inoculation of the blood culture media (BactAlert, BioMerieux, France) with an appropriate blood-sample volume (at least 1 ml) in appropriate conditions. Antibiograms were obtained using the disk diffusion method according to the National Committee for Clinical Laboratory Standards.[8] Empirical nosocomial sepsis antibiotic regimens were initiated according to Centres for Disease Control and Prevention (CDC) guidelines.[9] Antibiotics were changed in response to the results of the cultures and the sensitivity to the antibiotic test, both usually obtained within 36-72 hours. Antibiotic treatment was continued for 10 days in cases of infection documented by blood culture, 14-21 days in cases of meningitis, and 7 days in cases where infection was a robust risk but cultures were negative.[9,10] The results of the laboratory parameters (leukocytes, thrombocytes, I/T ratio, and CRP) for neonatal sepsis diagnosis, vital signs (axillary temperature, heart rate, oxygen saturation, and non-invasive blood pressure) were compared with blood-gas analysis results during the treatment with adjuvant agents.

The occurrence of an intraventricular haemorrhage (IVH), necrotising enterocolitis (NEC), and periventricular leukomalacia (PVL) in preterm neonates after treatment was recorded.

Systemic reactions such as tachycardia, bradycardia, tachypnoea, bradypnoea, hyper- or hypothermia, systemic hypo- or hypertension, and haemolysis using a peripheral blood smear during therapy were observed in the neonates.

The non-invasive arterial blood pressure and peripheral capillary oxygen saturation (SpO2) were obtained using a Masimo vital signs monitor (Masimo Corp., Irvine, California). Blood-gas analysis was performed using an automatic blood-gas analyser (Radiometer ABL90 FLEX analyser, Copenhagen, Denmark). The peripheral blood smears of all the neonates were evaluated by the same neonatologist.

The statistical analysis of the study was performed using the Number Cruncher Statistical System (NCSS) 2007 software. In addition to the descriptive statistical methods (mean, standard deviation) in the assessment of the data, an independent t-test was used in the comparison of groups, and the chi-square and Fisher's exact test was used in the qualitative data comparisons. The results were assessed at the significance level of $p<0.05$.

Results

Of the 41 neonates, 21(51.2%) were in group 1, and 20(48.8%) in group 2. Besides, 19(46.3%) participants were females and 22(53.7%) were males. All of the cases

Table-1: Demographic and clinical characteristics in VLBW neonates.

Demographic characteristics	PTX group (n:21) Mean±SD	PG group (n:20) Mean±SD	P*
Weeks of gestation	27.34±1,24	28.94±1.12	0.33
Birth weight (g)	1095.15±215.32	900-1470	0.26
Birth length (cm)	37,2±2.58	34.50±2.76	0.61
Head circumference (cm)	26.13±2.23	27.32±2.55	0.72
Initial treatment age (day)	11.23±5.35	12.6±6,36	0.77
Clinical characteristics n[a](%)			
Respiratory distress	5(23.8)	3(15)	0.50
Systemic hypotension	4(19)	5(25)	0.08
Tachycardia	9(42.8)	8(40)	0.03
Apnoea + bradycardia	8(38)	7(35)	0.04
Abdominal distension	9(42.8)	8(40)	0.03
Jaundice	3(14.2)	2(10)	0.17
Convulsion	2(9)	1(5)	0.30
Ventilation therapy and Total Parenteral nutrition	7	8	0.65
Inotropic support	3	3	0.71
Umbilical vein catheter (UVC)	11	13	0.41
Peripheral percutaneous central catheter (PICC)	6	4	0.52

[a]Cases could have more than one clinical sign.* t-test ,chi-square and Fisher Exact Test
VLBW: Very low birth weight
PTX: Pentoxifylline
PG: Pentaglobin
SD: Standard deviation.

Table-2: Pre-treatment stage parameters of neonates with nosocomial sepsis.

	PTX group (n:21) Mean±SD	PG group (n:20) Mean±SD	P*
Axillary temperature (°C)	35.82±0.22	35.92±0.41	0.17
I/T ratio	0.38±0.12	0.42±0.15	0.17
Leukocyte (/mm^3)	14818.1±3291.1	15565.2±2878.3	0.22
Thrombocyte (/mm^3)	94119.23±13256.2	95215.69±15341.3	0.40
Haemoglobin (g/dl)	10.11±1.27	10.18±1.11	0.42
CRP (mg/dl)	81.18±12.02	78.41±11.18	0.76
SBP (mmHg)	48.26±5.18	45.51±6.20	0.93
DBP (mmHg)	30.06±5.36	32.11±6.19	0.13
MBP (mmHg)	28.13±3.21	29.28±6.33	0.23
Heart rate/min	171.01±12.1	168.82±11.28	0.72
SpO2 (%)	88.10±3.60	89.26±4.11	0.76
pH	7.15±0.02	7.14±0.03	0.89
pCO_2	58.10±8.51	56.44±9.34	0.72
HCO_3 (mEq/l)	18.26±4.11	18.31±3.85	0.48
Base excess	-3.43±2.22	-3.46±2.51	0.70

PTX: Pentoxifylline
PG: Pentaglobin
I/T ratio: Immature/total ratio
CRP: C-reactive protein
SBP: Systolic blood pressure
DBP: Diastolic blood pressure
pH: potential of hydrogen
pCO2: Partial pressure of carbon dioxide
HCO3: Bicarbonate.

Table-3: Post-treatment stage parameters of neonates with nosocomial sepsis.

	PTX group (n:21) Mean±SD	PG group (n:20) Mean±SD	P*
Axillary temperature (°C)	36.8±0.25	36.92±0.51	0.22
I/T ratio	0.18±0.10	0.19±0.11	0.38
Leukocyte (/mm^3)	9265.11±2221.19	8968.22±2218.10	0.66
Thrombocyte (/mm^3)	148219.23±23236.53	151265.69±30341.11	0.87
Hemoglobin (g/dl)	10.21±1.47	11.18±1.21	0.20
CRP (mg/dl)	21.01±15.44	38.11±14.37	0.001
SBP (mmHg)	58.16±12.18	55.21±11.20	0.35
DBP (mmHg)	32.16±8.36	35.21±7.89	0.40
MBP (mmHg)	30.23±8.19	29.18±7.13	0.27
Heart rate/min	131.22±15.23	148.52±14.18	0.001
SpO2 (%)	91.20±4.20	90.36±3.31	0.76
pH	7.30±0.15	7.22±0.14	0.98
pCO_2	48.20±11.28	52.40±10.44	0.36
HCO_3 (mEq/l)	20.16±5.13	21.2±4.81	0.71
Base excess	-1.43±1.12	-1.44±1.31	0.48
Morbidities n(%)			
IVH, grade1	3(14.2)	2(10)	0.95
NEC, grade1	5(30.8)	4(23.1)	0.76
NEC, grade2	2(14.2)	2(10)	0.95
PVL , grade1	1(7.1)	2(5)	0.97
Symptomatic PDA	2(14.2)	1(5)	0.57

PTX: Pentoxifylline
PG: Pentaglobin
I/T ratio: Immature/total ratio
CRP: C-reactive protein
SBP: Systolic blood pressure
DBP: Diastolic blood pressure
MBP: Mean blood pressure
pH: potential of hydrogen
pCO2: Partial pressure of carbon dioxide
HCO3: Bicarbonate
IVH: Intraventricular haemorrhage
IVH: Intraventricular haemorrhage
NEC: Necrotising enterocolitis
PVL: Periventricular leukomalacia
PDA: Patent ductus asteriosus.

were delivered by Caesarean section (Table-1).

Of the 15(36.6%) cases that required invasive ventilation and parenteral nutrition, 6(40%) received inotropic support (dopamine 10 µg/kg/min) and intravenous replacement treatment. An umbilical vein catheter was present in 24(58.5%) cases, and 10(24.4%) cases had a peripheral percutaneous central catheter.

Vital signs, haematologic tables, peripheral blood smear left shift (I/T) ratio, and blood-gas parameters did not differ significantly (p>0.05) between the groups, but the CRP (mg/dl) and heart rate values decreased significantly after PTX treatment (Table-2).

Coagulase-negative staphylococci (CoNS) were the most

frequently isolated bacteria in the two groups (n=4; 19% vs. n=4; 20%). There was no difference in the isolated microorganisms (p>0.05). The neonates did not show any positive CSF cultures or urine cultures for the same organism.

There was no significant difference in IVH, NEC, PVL, or symptomatic patent ductus arteriosus (PDA) in the neonates when comparing the two groups (p>0.05). The mean duration of hospitalisation was 49.46±13.52 days for the PG group and 44.21±11.1 days for the PTX group neonates (p>0.05). All of the neonates during the study period were discharged from hospital (Table-3).

Discussion

Nosocomial sepsis particularly affects infants of VLBW and causes rapid death due to defective immune responses. Preliminary studies on PTX indicated encouraging PTX-related results in neonatal sepsis cases but there have been no related <1,500g neonates isolated with nosocomial sepsis. As a result, there is no clear consensus regarding PTX therapy use in sepsis. In these cases, every supportive treatment in addition to antibiotic therapy should be discussed in detail. Clinical and laboratory parameters of PG and PTX, which are frequently used in practice, should be evaluated and compared separately.

Two meta-analyses have shown that the addition of IgM-enriched IVIG to standard treatments has a highly significant effect on the reduction of mortality from sepsis; thus, adding IgM-enriched IVIG as an adjunct to standard therapy would seem to be advantageous.[7,8]

The present study detected that following PG therapy, that CRP, I/T, and heart rate decreased while capillary blood potential of hydrogen (pH) and base excess increased. Pentaglobin therapy had no negative effect on non-invasive arterial blood pressure, oxygen saturation, or other haematologic values. A 2015 Cochrane publication updated neonatal sepsis treatment, suggesting the efficacy of PTX in the treatment of neonatal sepsis. The Cochrane meta-analysis also showed that PTX therapy was associated with a decrease in mortality in NICUs after six trials were reviewed.[9] Shabaan et al. reported a useful supportive effect on antibiotic therapy in preterm infants with late-onset sepsis (LOS), but there was no effect on mortality and morbidity.[10]

In the present study, PG and PTX therapy was initiated in response to suspected clinical signs of sepsis and confirmed laboratory results of sepsis with no waiting for culture results. None of our cases were lost.

According to our study results, vital signs, haematologic tables, and peripheral blood smear left shift (I/T) ratio did not differ significantly (p>0.05) between the groups, but the CRP (mg/dl) values did significantly decrease after PTX treatment, and heart rate and blood-gas pH levels differed between the groups.

Haemolysis was reported as an important side effect of IVIG therapy in one study.[11] Pentoxifylline being associated with important adverse events is unusual, and no important adverse effects, such as thrombopoenia or haemorrhage, have been reported in critically sick preterm neonates with infection or NEC after treatment with PTX.[12]

No systemic reactions were observed during adjuvant therapy in the preterm neonates. We did not find any association with PG or PTX therapy major morbidities (PVL, IVH, and NEC) in preterm neonates. The total duration of hospitalisation was not found to differ between the groups.

In preterm infants, the most common pathogen associated with LOS is CoNS. In VLBW infants with LOS, the cases were caused by CoNS, gram-positive bacteria (Staphylococcus (S.) aureus, Enterococcus, group B streptococcus GBS), gram-negative bacteria (Escherichia (E.) coli, Klebsiella, Pseudomonas, Enterobacter, Serratia), and fungi (Candida albicans and parapsilosis).[13] In a retrospective study of 3,339 neonates with S. aureus infection in 348 NICUs, inadequate empiric antibiotic treatment (defined as not including $\geq$ 1 antibiotic with antistaphylococcal activity on day one of treatment) was associated with increased mortality among neonates with infection due to methicillin-resistant S. aureus (MRSA), but not among those with methicillin-sensitive S. aureus (MSSA) infection.[14] A similar study found that among neonates with LOS due to CoNS, vancomycin started on day one of therapy did not decrease 30-day mortality compared with delayed vancomycin therapy started after blood culture results, although it decreased the median duration of bacteraemia by a day.[15] In the present study, CoNS were the most frequently isolated bacteria in the two groups. There was no difference for isolated microorganisms.

The current had a few limitations as well. For instance, only VLBW premature infants with nosocomial sepsis were included and not healthy control group. Besides, the number of study participants were limited.

Conclusion

PTX treatment significantly decreased CRP and heart rate compared with PG treatment in <1,500g neonates with nosocomial sepsis and adverse short-time morbidity was not shown to be different in VLBW preterm infants.

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Conflict of Interest: None

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