ORIGINAL ARTICLE

Pentaglobin as an adjunct therapy in very low birthweight neonates with nosocomial sepsis

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Abstract

Objective: To evaluate the effect of pentaglobin treatment on clinical and laboratory parametres and the major morbidities in very low birthweight neonates with nosocomial sepsis before and after pentaglobin treatment.

Methods: The prospective interventional study was conducted from January 1 to December 31, 2010, at the neonatal intensive care unit (NICU) of the Bakirköy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey. Pentaglobin was initiated on the day of diagnosis of nosocomial sepsis to 13 pre-term neonates as a support therapy in addition to antibiotics; 5 ml/kg per day of pentaglobin was infused over a 4-hour period on 3 consecutive days. Clinical and laboratory parametres and major morbidities were recorded before and after pentaglobin treatment and compared using NCSS software.

Results: Of the total, 8(66%) were females and 5 (40%) males. Following pentaglobin therapy, the immature-to-total neutrophil ratio and C-reactive protein levels were significantly decreased, and the capillary pH and base excess were significantly increased ($p<0.05$). The axillary temperature, non-invasive blood pressure, haemoglobin, leukocyte, and thrombocyte values did not significantly differ before and after treatment ($p>0.05$). Coagulase-negative staphylococci (n=3; 23%), Klebsiella pneumoniae (n=2; 15.3%), and Pseudomonas aeruginosa (n=1; 7.7%) were identified in blood cultures. The presence of intraventricular haemorrhages, necrotising enterocolitis, periventricular leukomalacia, and patent ductus arteriosus was not changed following the treatment. Adverse effects and mortality were not observed during or after the therapy.

Conclusion: Pentaglobin treatment of nosocomial sepsis could be used as an adjunct therapy without any adverse short-term reactions, even in very low birthweight pre-term infants.

Keywords: Pentaglobin, Nosocomial sepsis, NICU, Very low birthweight. (JPMA 63: 1353; 2013)

Introduction

The severe outcome of nosocomial sepsis, despite the advances in perinatal and neonatal care and the use of potent antibiotics, is related to reduced neonatal immune defenses and complex interactions between the infecting microorganism and the host response.[1] Neonates, especially premature neonates (<37 completed weeks of gestation) requiring intensive care support constitute a highly vulnerable population at extreme risk for nosocomial infection.[2] The incidence of nosocomial sepsis ranges from 6-22% in neonates who survive 48 or more hours in a neonatal intensive care unit (NICU).[2] Bacterial sepsis in neonate is a clinical syndrome characterised by clinical signs of infection (respiratory distress, apnea, abdominal distention, etc.) and accompanied by bacteraemia in the first month of life. Neonates whose bacterial culture results are negative and having significant clinical signs of infection and supporting laboratory parametres (C-reactive protein [CRP], the immature-to-total neutrophil ratio [I/T ratio], etc.) are treated with appropriate antibiotics for presumed sepsis for 10 days if the clinical condition of the infant remains uncertain and suspicion of an infectious process remains.[2-4]

There is an ongoing debate about the efficacy of intravenous human immunoglobulin (IVIG) in the treatment of neonatal sepsis. To date, several meta-analyses/systematic reviews have been published on the adjunct use of polyclonal IgG IVIG or IgM-enriched IVIG in the prevention or treatment of neonatal sepsis. IgM has the capacity to induce the pronounced activation of the complement system. IgM activates 100-400-fold more complement than IgG and is thus a more effective killer of bacteria. The opsonisation of bacteria by IgM is also approximately 1000-fold greater than IgG.[5] Several studies have compared the effect of standard IVIG to an IgM-enriched IVIG preparation in the treatment of neonatal sepsis.[6-9] However, no reports have evaluated the effect of IgM-enriched IVIG preparations on

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laboratory and clinical parametres in neonatal nosocomial sepsis.

The current study compared clinical and laboratory parametres and major morbidities (intraventricular haemorrhage [IVH], necrotising enterocolitis [NEC], periventricular leukomalacia [PVL], and patent ductus arteriosus [PDA]) before and after pentaglobin therapy in nosocomial sepsis managed in an NICU.

Patients and Methods

The prospective interventional study was conducted from January 1 to December 31, 2010, at the neonatal intensive care unit (NICU) of the Bakirköy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey. The neonates with birthweight <1500g (very low birthweight) who had presumed or proven nosocomial sepsis and had been treated with the intravenous IgM-enriched IVIG preparation Pentaglobin® (38 g/l IgG, 6 g/l IgM, and 6 g/l IgA; Biotest, Dreieich, Germany; 5 ml/kg per day over 4 hours for 3 consecutive days) as an adjunct therapy to a classical nosocomial sepsis antibiotic treatment protocol were selected for the study.

Proven neonatal sepsis is defined as having a positive blood culture accompanied by systemic signs of infection (respiratory distress, apnoea, cyanosis, abdominal distention, etc.) in the first month of life. Presumed neonatal sepsis is defined as having negative blood, urine, and cerebrospinal fluid (CSF) cultures, but having any significant clinical signs of infection plus supporting laboratory parametres (I/T ratio greater than 0.2; a total leukocyte count of either $<5x10^9$/l or $>15x10^9$/l; thrombocytopaenia (<150,000/mm^3); and a 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 CSF, and bacterial growth in a CSF culture.[2,3,10]

The blood culture results were evaluated after the inoculation of blood culture media (BactAlert, BioMerieux, France) with an appropriate volume of a blood sample (at least 1ml) under the appropriate conditions. Antibiograms were obtained with the disk diffusion method according to the National Committee for Clinical Laboratory Standards.[11] Empirical nosocomial sepsis antibiotic regimens were initiated according to the Centre for Disease Control and Prevention (CDC) guidelines.[12] Neonates who were thought to have presumed nosocomial sepsis were treated with 5ml/kg of an intravenous IgM-enriched IVIG preparation (Pentaglobin®) for 3 consecutive days with simultaneous antibiotic treatment shortly after the initial blood, urine, and/or CSF culture studies. Antibiotics were changed according to the results of the specimen culture and the in vitro sensitivity to antibiotic test, which were usually obtained within 48-72 hours. Antibiotic therapy was continued for 10 days in cases of sepsis documented by blood culture, 14-21 days in cases of meningitis, and 7-10 days in cases in which sepsis was a strong possibility, but cultures were negative.[12,13]

The results of laboratory values (leukocytes, thrombocytes, I/T ratio, and CRP) were compared for neonatal sepsis diagnosis with the vital signs (axillary temperature, heart rate, oxygen saturation, and arterial blood pressure), and the arterial blood gas results before and after treatment with pentaglobin.

The occurrence of IVH, NEC, PVL and PDA in pre-term neonates before and after pentaglobin treatment was recorded.

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

The non-invasive arterial blood pressure and blood oxygen saturation (SpO_2) were obtained using a Nihon Kohden vital signs monitor. An arterial blood gas analysis was performed with an automatic blood gas analyser (Radiometer ABL800 FLEX analyser, Copenhagen, Denmark). The peripheral blood smears of all the patients were evaluated by the same physician. Bacterial culture results of these neonates were recorded for any isolated pathogen. Permission to conduct the study was obtained from the ethical committee of the hospital, and informed consent was also obtained from the parents.

Statistical analysis of data was done using the NCSS 2007 software. The results were analysed with the Wilcoxon test and the Chi-square test for descriptive methods. A $p<0.05$ was considered statistically significant.

Results

A total of 13 neonates, including 8 (60%) females and 5 (40%) males, were included in the study. All of the cases were delivered by C-section. Proven sepsis was seen in 6 (46%) neonates and 7 (54%) neonates were treated for suspected sepsis. Demographic and clinical characteristics of the neonates were noted (Table-1). Of the 5(40%) cases that required invasive ventilation and parenteral nutrition, 3(60%) received inotropic support

(dopamine and/or dobutamine, 5-10µg/kg/minute) and intravenous replacement treatment. An umbilical vein catheter was present in 4(30.7%) cases, and 5(40%) cases had a peripheral percutaneous central catheter. The comparison of the vital signs (body temperature, noninvasive arterial blood pressure, and SPO_2), haematological tables (white blood cell, haemoglobin, and platelet levels), peripheral blood smear left shift (I/T) ratio, and CRP values before and after therapy were also noted (Table-2). The vital signs, haematological table, and I/T ratio did not differ significantly ($p>0.05$) before and after the treatment, but the CRP values were significantly decreased after treatment ($p<0.004$).

Table-1: Demographic and clinical characteristics of the neonates.

Demographic characteristics	Mean	SD
Weeks of gestation	29.87	3.42
Birth weight (g)	1026.67	403.31
Birth length (cm)	35.20	3.84
Head circumference (cm)	27.40	1.87
Initial pentaglobin treatment age (day)	13.60	8.13

Clinical characteristics*	Proven sepsis n(%)	Suspected sepsis n(%)	P**
Respiratory distress	1 (7.6)	1 (7.6)	NS
Systemic hypotension	4 (30.7)	3 (23)	NS
Tachycardia	3 (23)	3 (23)	NS
Apnoea + bradycardia	4 (30,7)	3 (23)	NS
Abdominal distension	5 (38.4)	2 (15.3)	NS
Jaundice	2 (15.3)	1 (7.6)	NS
Convulsion	1 (7.6)	-	NS

*The study cases could have more than one clinical sign.** Chi-Square test. NS: Not significant.

Table-2: Comparison of clinical and laboratory parametres.

	Pentaglobin treatment (n=13)		
	Before mean±SD	After mean±SD	P*
Axillary temperature (°C)	36.59±0.14	36.67±0.41	0.903
I/T ratio$^{\alpha}$	0.42±0.19	0.32±0.51	0.021
Leukocyte (/mm^3)	13313.33±8946.02	15178.57±7859.95	0.140
Thrombocyte (/mm^3)	342530.33±131000.59	422710.43±178920.65	0.204
Hemoglobin (g/dl)	10.52±2.43	10.89±2.84	0.477
CRP (mg/dl)$^{\beta}$	6.23±6.44	1.23±1.56	0.004
SBP (mmHg)£	65.23±11.45	68.08±8.08	0.575
DBP (mmHg)†	41.54±8.68	42.5±7.43	0.894
MBP (mmHg)††	49.75±14.73	51.38±9.99	0.666
Heart rate/min	161.73±15.67	137.73±8.81	0.01
SpO2 (%)	90.18±18.51	95±4.69	0.917
pH	7.31±0.1	7.38±0.04	0.007
pO_2	72.14±6.88	78.79±16.88	0.300
pCO_2	43.71±10.24	44.14±5.65	0.729
HCO_3 (mEq/l)	23.83±4.02	24.5±3.92	0.650
Base excess	-2.64±2.26	1.19±3.61	0.003

*Wilcoxon test; αI/T ratio: Immature/total ratio; £SBP: Systolic blood pressure; †DBP: Diastolic blood pressure; ††MBP: Mean blood pressure; βCRP: C-reactive protein.

Table-3: Pentaglobin treatment (PGT) effect on morbidity in pre-tem neonates.

		Before PGT$^{\alpha}$ n(%)	After PGT n(%)	P*
Intraventricular hemorrhage, grade	1	2(15)	2(15)	NS
	2	1(7)	1(7)	NS
	4	1(7)	1(7)	NS
Necrotizing enterocolitis, grade	1	7(53)	3(23)	NS
Periventricular leukomalacia, grade	1	2(15)	2(15)	NS
	3	1(7)	1(7)	NS
Symptomatic patent ductus arteriosus		1(7)	1(7)	NS

*Chi-square test. NS: not significant.

Coagulase-negative staphylococci (CoNS) was the most frequent isolate and was found in 3 (23%) subjects. The other isolated micro-organisms included Klebsiella pneumoniae in 2 (15.3%) subjects and Pseudomonas aeruginosa in 1 (7.7%). These neonates did not have any positive CSF cultures or urine cultures for the same organism. No growth was observed in the other haemocultures.

The major morbidities in the pre-term neonates before and after the treatment were also noted (Table-3). There was no significant difference in IVH, NEC, PVL, or symptomatic PDA in the neonates.

No systemic reactions were observed during the therapy in the neonates. The mean total duration of hospitalisation was 53.64±16.92 days for pentaglobin-treated pre-term neonates. No neonate died during the study period and all were discharged from hospital.

Discussion

Neonatal nosocomial sepsis is a major cause of death and complications despite antibiotic treatment for pre-term neonates in NICUs. Effective adjunct treatments are needed. Meta-analyses of trials of intravenous immunoglobulin for suspected or proven neonatal sepsis suggest a reduced rate of death from any cause, but the trials have been small and have varied in quality.[14] A number of studies support the administration of IVIG along with supportive and antibiotic therapy in neonatal sepsis.[14-16] According to the International Guidelines for Management of Severe

Sepsis and Septic Shock in 2008, there is a grade 2C recommendation for the use of polyclonal immunoglobulin in paediatric sepsis syndrome.[17] Based on these guidelines, the administration of intravenous polyclonal immunoglobulin has been reported to reduce the mortality rate and is a promising adjuvant in the treatment of sepsis and septic shock in neonates.[18] Apart from the Cochrane database in 2010, there is insufficient evidence to support the routine administration of IVIG to prevent mortality in infants with suspected or subsequently proven neonatal infection.[8] Moreover, the International Neonatal Immunotherapy Study (INIS) Collaborative Group reported in 2011 that therapy with IVIG had no effect on the outcomes of suspected or proven neonatal sepsis.[19] For these reasons, some centres use pentaglobin as an adjunct therapy for nosocomial sepsis in NICUs. One recent meta-analysis has also shown that the addition of IgM-enriched IVIG to standard treatment 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]

The theoretical reasons for using IVIG in neonatal sepsis are strong, but the evidence for using IgM-enriched IVIG is even stronger, particularly in gram-negative sepsis.[20,21] Thus, the earlier IgM therapy is instituted, the less likely lipid A-induced tissue damage will occur. In our study, early pentaglobin therapy was initiated upon the suspected clinical signs of sepsis and confirmatory laboratory results of sepsis without waiting for any culture results, and none of our cases were lost. According to our study results, after pentaglobin therapy, CRP, I/T, and heart rate decreased, while capillary blood pH and BE increased. Moreover, pentaglobin therapy had no negative effect on non-invasive arterial blood pressure, oxygen saturation, or other haematologic values. These clinical and laboratory findings may show that IgM is more potent against the septic process, possibly because of its size, which permits a more efficient inhibition of the lipopolysaccharide core on the bacterial surface during neonatal sepsis.

In developed countries, ***Listeria monocytogenes***, ***Escherichia coli***, ***Staphylococcus aureus***, ***Staphylococcus epidermidis*** (CoNS), and ***gram-negative enteric bacilli*** are the most common causes of nosocomial sepsis in the NICU. However, in developing countries, these bacteria are replaced by gram-negative enteric bacilli (e.g., ***Klebsiella spp.***, ***Enterobacter spp.***, and ***Serratia spp.***), ***CoNS, E. coli***, and ***S. aureus***.[22,23] Moreover, recent studies in developing countries also identified ***Candida spp.*** and ***Pseudomonas spp.*** in nosocomial sepsis.[24,25] In our study, the most frequently isolated micro-organism was CoNS, and the other isolated micro-organisms were Klebsiella pneumoniae and ***Pseudomonas aeruginosa***.

Haemolysis was reported as an important side effect of IVIG therapy in one study.[26] However, we did not observe any systemic reaction or any haemolysis during pentaglobin therapy.

To our knowledge, no reports have evaluated the association of pentaglobin therapy with major morbidities, such as PVL, IVH, and NEC, in pre-term neonates. This study did not identify an association between pentaglobin therapy and the morbidities mentioned above. Other major morbidities, such as bronchopulmonary dysplasia and retinopathy of prematurity, were not recorded because of the lower postnatal age of the neonates during the therapy.

Limitation of this study was the lack of a control group treated only by appropriate antibiotics for sepsis.

Conclusion

Pentaglobin treatment of neonatal nosocomial sepsis could be used as an adjunct therapy without any adverse short-term reactions even in VLBW pre-term infants.

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