The influence of IgM-enriched immunoglobulin therapy on neonatal mortality and hematological variables in newborn infants with blood culture-proven sepsis

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SUMMARY: Abbasoğlu A, Ecevit A, Tuğcu AU, Yapakçı E, Tekindal MA, Tarcan A, Ecevit Z. The influence of IgM-enriched immunoglobulin therapy on neonatal mortality and hematological variables in newborn infants with blood culture-proven sepsis. Turk J Pediatr 2014; 56: 267-271.

The aim of this study was to determine the effects of adjuvant immunoglobulin M (IgM)-enriched intravenous immunoglobulin (IVIG) therapy on mortality rate, hematological variables and length of hospital stay in newborn infants with blood culture-proven sepsis.

Demographic and clinical features and outcome measures of 63 newborn infants with blood culture-proven sepsis were documented retrospectively from the medical records. The patients were divided into two groups according to their treatment history. The patients in Group 1 received antibiotic therapy only and the patients in Group 2 received both antibiotic and adjuvant IgM-enriched IVIG.

The study revealed that mortality rates were 28.1% and 12.9% in Group 1 and Group 2, respectively. The mortality rate was lower in Group 2, but the difference between the two groups was not statistically significant (p=0.21). Coagulase-negative Staphylococcus was the most common type of bacteria isolated from the blood culture in both groups. When changing laboratory results were compared between the two groups, hemoglobin, leukocyte count and C-reactive protein levels were different during the first three days of antibiotic treatment.

Our study revealed that if diagnosed at an early stage and treated aggressively with appropriate and effective antibiotics, adjuvant IgM-enriched IVIG treatment has no additional benefits in neonatal sepsis.

Key words: intravenous immunoglobulin, neonatal sepsis.

The morbidity and mortality from neonatal sepsis remain high despite the use of effective bactericidal antimicrobial agents and technologically advanced intensive care services in patients with life-threatening diseases[1]. Therefore, adjuvant therapies such as intravenous immunoglobulin (IVIG), pentoxifylline and cytokines may provide additional support[2].

Because of their relatively immature immune system, newborn infants are considered to be immunocompromised. Humoral immunity is provided primarily by maternal immunoglobulin G (IgG) antibodies across the placenta. Transplacental transfer of maternal antibodies to the fetus usually begins after 32 weeks of gestation, but endogenous synthesis of antibody does not begin until about 24 weeks after birth[3]. Infusion of IVIG increases low levels of serum immunoglobulin and enhances neonatal host defenses, providing opsonic antibody against neonatal pathogens that enhance phagocytosis and killing of bacteria by neutrophils[4].

Intravenous immunoglobulin (IVIG) contains more than 95% unmodified IgG, which has functionally intact Fc-dependent effector functions and only trace amounts of immunoglobulin A (IgA) or immunoglobulin M

(IgM)[5]. Different commercial IVIG preparations have been described in sepsis studies, including those containing over 96% IgG or IgM-enriched. The IgM-enriched preparation (Pentaglobin®, Biotest Pharma, Germany) contains 38 g/L IgG, 6 g/L IgM, and 6 g/L IgA. The IgM-enriched IVIG has been accepted as more physiological when compared with human plasma, which contains all three immunoglobulin classes[6].

Intravenous immunoglobulin (IVIG) has been used for the prevention and treatment of neonatal sepsis since the 1980's, but its usage remains controversial[7]. Some studies found significant differences in clinical variables and outcome with IgM-enriched immunoglobulin treatment, whereas others did not. There remains an ongoing debate about the efficacy of IVIG in the treatment of neonatal sepsis.

In this retrospective study, we aimed to determine the effects of adjuvant IgM-enriched IVIG therapy on mortality rate, hematological variables (1-3 days) and length of hospital stay in newborn infants with blood culture-proven sepsis.

Material and Methods

This study was carried out in a tertiary care neonatal unit in Başkent University in Turkey, from 2006-2012. Gender, gestational week, age at proven sepsis, complete blood count, C-reactive protein (CRP) (reference values: 0-5 mg/L), microorganisms isolated from blood culture, and antibiotic treatment were documented from the medical records. Clinical symptoms such as hypothermia, hyperthermia, apnea, tachypnea, tachycardia, bradycardia, hypotonia, hypotension, inotropic drug use, supplemental oxygen, presence of central catheters, total parenteral nutrition, and signs of convulsion were also reviewed based on the medical records.

Procalcitonin, CRP, interleukin-6, interleukin-8, tumor necrosis factor-alpha, CD11b, and neutrophil CD64 have been used recently for the diagnosis of neonatal sepsis. Blood culture is the gold standard test for the definitive diagnosis of neonatal sepsis[8]. For this study, sepsis was defined as a positive blood culture with one or more clinical symptoms. Because of increasing antibiotic resistance, adjuvant therapies such as IVIG, pentoxifylline, cytokines, and granulocyte transfusions are also used for treatment[2]. In our study, we used IgM-enriched IVIG as an adjuvant treatment. The patients were divided into two groups according to their treatment history. The patients in Group 1 received antibiotic therapy only and the patients in Group 2 received both antibiotic and adjuvant IgM-enriched IVIG (Pentaglobin® Biotest Pharma, Dreieich, Germany), which was started on the day of the sepsis diagnosis. IgM-enriched IVIG was infused intravenously over a period of 6 hours at a dose of 5 ml/kg/day, and repeated for three consecutive days.

The statistical software SPSS (Statistical Package for the Social Sciences, Version 20, Chicago, IL, USA) was used for the calculations. All values are presented as mean±standard deviation and mean (maximum-minimum) percent and frequencies. Repeated measures of analysis of variance were the necessary pre-conditions analyzed by Mauchy's sphericity test and Box's test of equality of covariance matrices. If parametric tests (factorial design for repeated measures analysis) did not provide the preconditions, Greenhouse-Geisser (1959) or Huynh-Feldt (1976) was used for corrections to the degrees of freedom. The corrected Bonferroni test was used for multiple comparisons. Categorical data were analyzed with Fisher's exact test and chi-square test. A value of $p<0.05$ was considered statistically significant.

Results

In this study, 63 cases in total were evaluated. Group 1 consisted of 31 newborn infants and Group 2 of 32 infants. The demographic variables and outcome measures of both groups are shown in Table I.

The study revealed that mortality rates were 28.1% and 12.9% in Group 1 and Group 2, respectively. The mortality rate was lower in Group 2, but the difference between the two groups was not statistically significant ($p=0.21$).

The microorganisms isolated from the blood culture are shown in Table II. Coagulase-negative Staphylococcus and *Klebsiella pneumoniae* were the most common types of bacteria isolated from the blood culture in both groups.

Clinical symptoms, usage of parenteral nutrition and inotropic agent and the presence of central catheter were similar in both groups (Table III).

Table I. Demographic Features and Outcome Measures

Baseline characteristics	Group 1	Group 2	p-value
Gender (female/male)	18/14	16/15	0.80
Gestational age (weeks)	31.3±4.6	29.8±4.1	0.19
Mode of delivery (vaginal delivery/cesarean section)	10/22	7/24	0.57
Birth weight (g)	1706.8±818.9	1436.8±723.6	0.17
Body weight (g)	1706.8±144.7	1436.8±129.9	0.13
Mean age (days)	24.4±25.7	16.0±10.6	0.09
Length of hospitalization (days)	55.4±33.6	45.5±25.9	0.19

Table II. Distribution of Blood Culture Bacterial Isolates in the Two Groups

Organisms	Group 1	Group 2	Total
Coagulase-negative staphylococci	14	10	24
Staphylococcus epidermidis	1	5	6
Klebsiella pneumoniae	10	9	19
Pseudomonas aeruginosa	2	0	2
Staphylococcus aureus	2	1	3
Acinetobacter baumannii	1	2	3
Enterococcus faecium	1	0	1
Escherichia coli	1	1	2
Serratia marcescens	0	2	2
Candida albicans	0	1	1
Total	32	31	63

When changing laboratory results were compared between the two groups, hemoglobin, leukocyte count and CRP levels were different during the first three days of antibiotic treatment (Table IV). Platelet counts did not change during treatment in either group.

Discussion

In this study, IgM-enriched IVIG had no impact on hematological variables, hospital length of stay or mortality in newborn infants with culture-positive sepsis.

Generally, IgM is a more potent immunoglobulin in the treatment of gram-negative sepsis due to more efficient blockade of lipopolysaccharide core on the bacterial surface and activation of complement systems. Thus, especially early IgM therapy can decrease lipid A-induced tissue damage[9].

There are many studies about the use of IgM-enriched IVIG as an adjuvant therapy, with conflicting results. Norrby-Teglund et al.[6] conducted a systematic review and meta-analysis on the use of polyclonal IgM-enriched IVIG in severe sepsis in adult, pediatric and neonatal patients, and found that addition of IgM-enriched IVIG to the standard treatment significantly reduced mortality from sepsis. Kreymann et al.[10] analyzed studies using either polyclonal IgG IVIG or polyclonal IgM-enriched IVIG in neonates with sepsis and showed significant reduction in mortality with both types of IVIG. Erdem et al.[11] also evaluated the use of IgM-enriched immunoglobulin for the treatment of sepsis in 44 preterm infants. The mortality rates in the control group (37.5%) and immunotherapy group (30.0%) were not found significantly different. An update on the Cochrane Database showed that the use of IgM-enriched IVIG is still insufficient to support a conclusion of benefit on neonatal sepsis[12]. In our study, mortality rates were 28.1% and 12.9% in Group 1 and Group 2, respectively, and there was no statistically significant difference between the two groups ($p>0.05$).

Table III. Clinical Features, Parenteral Nutrition, Need for Inotropic Support, and Presence of Central Catheter at Presentation

Clinical profile	Group 1	Group 2	p-value
Hypoactivity	9/32	11/31	0.59
Hypothermia	0/32	3/31	0.11
Hyperthermia	7/32	2/31	0.14
Apnea	9/32	11/31	0.59
Tachypnea	2/32	2/31	1.00
Bradycardia	6/32	6/31	1.00
Tachycardia	6/32	4/31	0.73
Hypotonia	3/32	27/31	1.00
Convulsion	2/32	1/31	0.50
Total parenteral nutrition	16/32	16/31	1.00
Central catheter	15/32	16/31	0.80
Inotropic support	10/32	9/31	1.00

Table IV. Hematological Variables in the Two Groups during Treatment

		Pre-Treatment	Treatment Day 1	Treatment Day 3	p-value
Hemoglobin	Group 1	12.87±2.93	12.71±2.22	12.26±2.31	0.384
	Group 2	13.80±2.97	13.01±2.31	12.32±2.38	
Leukocyte	Group 1	14214.68±6329.58	18253.12±8266.79	18678.12±8068.02	0.082
	Group 2	12804.83±8899.20	13099.67±8937.75	17494.19±9220.70	
Platelet	Group 1	256451.87±183072.76	241340.62±196582.57	251012.50±180627.36	0.783
	Group 2	237238.70±150369.53	209016.12±147349.54	201945.16±194351.23	
CRP	Group 1	31.32±41.74	82.73±62.55	50.47±44.86	0.414
	Group 2	19.18±36.63	61.74±39.98	46.76±49.11	

CRP: C-reactive protein.

Intravenous immunoglobulin (IVIG) is generally a safe medication, but it does inherit some risks of serious adverse effects, particularly hematologic toxicities such as hemolytic anemia, arterial and venous thrombosis, and cytopenia[13]. Haque et al.[9] compared the time interval from abnormal laboratory results at the beginning of treatment until their normalization among the standard IVIG, IgM-enriched IVIG and control groups in the treatment of neonatal sepsis. The time lapse to normalization of values was 19.1 hours for leukocyte count, 25.6 hours for platelet count and 53.2 hours for CRP in the IgM-enriched immunoglobulin group. They found that leukocyte counts and immature to total neutrophil ratio (I/T ratio) improved faster in the IgM-enriched IVIG group compared with either the standard IVIG or the control group in neonatal sepsis. In our study, IgM-enriched immunoglobulin did not impact hemoglobin, leukocyte, platelet counts, or CRP levels. There were no statistically significant differences between the two groups ($p>0.05$). These differences can be explained by the difference in the design of these two studies. The study of Haque et al.[9] was composed of both culture-proven and suspected sepsis cases, whereas our study was composed of only culture-proven neonatal sepsis cases. The observation regarding the length of hospital stay was similar to some other studies[14,15]. Tugrul et al.[14] observed that length of stay in the intensive care unit was similar between the IgM-enriched IVIG and control groups among septic adult patients. Neilson et al.[15] reported that IgM-enriched IVIG reduced the risk of mortality of severe sepsis in adult patients but had no effect on intensive care unit length of stay. In our study, the length of hospital stay was found similar between the two groups. The length of hospital stay was 55.4±33.6 and 45.5±25.9 days in Groups 1 and 2, respectively, and there was no statistically significant difference between the two groups

($p>0.05$).

The clinical trials of Haque et al.[9,16] and meta-analysis of Norrby-Teglund et al.[6] showed that patients with gram-negative sepsis had a significantly lower rate of mortality after IgM-enriched IVIG compared with the control groups. In our study, although the patients who received IgM-enriched IVIG had a lower mortality rate compared with patients who only received antibiotic treatment, no statistically significant difference was found. Approximately half of the patients in each group suffered from gram-positive sepsis, which is why there was no statistically significant difference in neonatal mortality.

Our study revealed that if diagnosed at an early stage and treated aggressively with appropriate and effective antibiotics, adjuvant IgM-enriched IVIG treatment has no additional benefits in especially gram-positive neonatal sepsis.

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