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THE USE OF IgM – ENRICHED INTRAVENOUS IMMUNOGLOBULIN FOR THE TREATMENT OF NEONATAL SEPSIS IN PRETERM INFANTS*

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SUMMARY: Erdem G, Yurdakök M, Tekinalp G, Ersoy F. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). The use of IgM-enriched intravenous immunoglobulin for the treatment of neonatal sepsis in preterm infants. Turk J Pediatr 1993; 35: 277-281.

The value of IgM-enriched immunoglobulin therapy in 44 preterm infants with neonatal sepsis was evaluated in a prospective randomized study. All infants received antibiotic therapy and fresh plasma and / or whole blood transfusions. Twenty randomly-chosen infants were allocated to receive 5 ml / kg / d of IgM-enriched immunoglobulin intravenously for three days. Although the mortality rate in preterm infants whose gestational ages were 31-34 weeks in the immunotherapy group was slightly lower than in the control group, the general mortality rate from sepsis in the control group (9 / 24) and in the immunotherapy group (6 / 20) showed no statistically significant difference (37.5% vs 30.0%, $p < 0.05$). *Key words: intravenous immunoglobulin, neonatal sepsis, fresh plasma.*

The high mortality and morbidity rates of neonatal sepsis in preterm infants despite the development of new generation broad-spectrum antimicrobial drugs and improved perinatal care have led to the search for other treatment modalities[1]. It has been reported that intravenous immunoglobulin IVIg therapy in conjunction with antibiotic therapy significantly reduces mortality from neonatal sepsis[2]. We report the results of our study using IgM-enriched IVIg in the treatment of this condition.

Material and Methods

Fourty-four preterm infants between the gestational ages of 31 and 37 weeks who had sepsis but no severe congenital malformations, inborn error of metabolism, intrauterine infection or intracranial hemorrhage were enrolled in the study.

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The early diagnosis of neonatal sepsis was made by using Töllner's Sepsis Scoring System[3]. Prior to therapy, blood samples were drawn for culture, white blood cell count and peripheral blood smear. The cases having a positive blood culture were classified as "proved sepsis" and the others as "suspected sepsis".

All infants with neonatal sepsis received supportive therapy including daily fresh frozen plasma and / or blood transfusions, as well as antibiotic therapy. The initial antibiotics used in all infants were penicillin (100.000 U / kg / d) and amikacin (15 mg / kg / d) until culture results were available. Antibiotics were changed according to susceptibility-test results. Antibiotic therapy was continued for at least ten days regardless of the culture result.

Twenty infants with sepsis (immunotherapy group) randomly were chosen to receive 5 ml / kg / d IgM - enriched IVIg (Pentaglobin, Biotest Pharma, Frankfurt, Germany) consisting of IgM 6 mg, IgA 6 mg and IgG 38 mg per 1 ml. This therapy was administered for three successive days. For each infant the outcome of sepsis was recorded and the Student's *t* test was used to compare results.

Results

The two groups were comparable with regard to infants' gestational age, sex, birth weight, history of prolonged rupture of membranes and Apgar score at five minutes. The blood culture was positive in 15 infant (75.0%) in the immunotherapy group, and 15 (62.5%) in the control group (Table I).

Although the mortality rate in preterm infants with gestational ages of 31-34 weeks in the immunotherapy group was lower than that in the control group, this difference was not statistically significant. The outcomes of the infants in both groups were also similar; nine (37.5%) and six (30.0%) infants died in the control and immunotherapy groups, respectively (Table I).

Discussion

IVIg therapy has been recommended for prophylactic use in infants at high risk of developing sepsis (e.g. < 32 weeks or < 1500 g) or as a "rescue" therapy for infants who already have sepsis[2]. The results of prophylactic therapy are controversial[4-8], as two of the trials concluded that prophylaxis could not reduce septicemia in preterm infants[7,8].

The two reported "rescue" trials showed improved survival in septic neonates[9,10]. Sidiropoulos et al[9] completed a randomized open "rescue" trial with intravenous IgG (Sandoglobulin) in 22 preterm infants with confirmed sepsis. Four of the nine infants (44%) in the control group and one of the 13 infants (8%) in the group receiving IVIg died ($p < 0.04$). Haque et al[10] conducted a double-blind "rescue" trial with intravenous IgM-enriched immunoglobulin (Pentaglobin) in sixty preterm infants who had suspected sepsis which was confirmed bacteriolo-

Table I: Selected Clinical Findings and Outcomes of Preterm Infants with Neonatal Sepsis Who Had or Had Not Received Intravenous Immunoglobulin

	Control Group	Immunotherapy Group
No.	24	20
Male / Female	17 / 7	13 / 7
Gestational age (wk)	34.9 ± 1.7	34.4 ± 1.9
Birth weight (g)	2050 ± 369	2085 ± 352
No. of infants SGA	5 (20.8%)	3 (15.0%)
No. of infants with PROM	2 (8.3%)	6 (30.0%)
Apgar score below 7 at 5 min	6 (25.0%)	9 (45.0%)
Blood culture results		
Escherichia coli	6	7
Klebsiella pneumoniae	2	4
Pseudomonas aeruginosa	2	1
Staphylococcus aureus	4	2
Staphylococcus epidermidis	1	1
Mortality		
Gestational ages		
31-34 wk	5 / 10 (50.0%)	3 / 10 (30.0%)
35-37 wk	4 / 14 (28.6%)	3 / 10 (30.0%)
Proved sepsis	7 / 16 (43.8%)	5 / 15 (33.3%)
Suspected sepsis	2 / 8 (25.0%)	1 / 5 (20.0%)
Total	9 / 24 (37.5%)	6 / 20 (30.0%)

Abbrevations:
SGA : small for gestational age.
PROM : prolonged rupture of membranes (longer than 24 hours).

gically in 44. Mortality from sepsis was significantly higher: six of the 30 infants (20%) in the control group, and one of the 30 (3%) in the immunoglobulin-treated group ($p < 0.001$).

We used the same IgM-enriched immunoglobulin preparation (Pentaglobin) as did Haque et al[10] to treat preterm infants with sepsis in this study. Although Haque et al concluded that IgM-enriched immunoglobulin therapy in conjunction with antibiotic therapy significantly reduces mortality from neonatal sepsis in preterm infants, our findings do not support this conclusion.

Our findings may be explained by the use of fresh frozen plasma or whole blood in this study. There has been no prospective randomized controlled study using fresh frozen plasma or whole blood transfusions as adjuvant therapy in infected

newborn infants, but this modality is widely used in all countries. The rationale for the use of such therapy is to improve peripheral and pulmonary perfusion and to enhance humoral and cellular immunity and complement dependent opsonization in the infected newborn infant[11].

Although several investigators[9,10] have suggested that combining IVIg with antibiotics might be more effective than using antibiotics alone, the results of their studies should be cautiously interpreted because: 1) there is a lack of expanded trials from different parts of the world; 2) there is a lack of type-specific antibodies against microorganisms commonly seen in developing countries in IVIg preparations prepared from donors living in western countries[12]; 3) high doses of IVIg seem to block the reticuloendothelial system[13]; 4) in animal models, it has been shown that high doses of IVIg may cause blockage of neutrophils or bacterial receptors[14]; 5) high doses of IVIg may impair the therapeutic benefit of penicillin G against neonatal sepsis[15]; and 6) the risk of acquiring hepatitis C is higher in infants receiving IVIg manufactured from a few thousand donations than fresh plasma or whole blood transfusions from one or a few donors[16]. In addition, IVIg treatment is very expensive. So, we are waiting for the results of additional clinical trials before making a conclusion.

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