The Turkish Journal of Pediatrics 1997; 39: 341-345

INTRAVENOUS IMMUNOGLOBULIN FOR SEPSIS PREVENTION IN PRETERM INFANTS*

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SUMMARY: Tanzer F, Yazar N, Hakgüdener Y, Kafalı G. (Department of Pediatrics, Cumhuriyet University Faculty of Medicine, Sivas, Turkey). Intravenous immunoglobulin for sepsis prevention in preterm infants. Turk J Pediatr 1997; 39: 341-345.

The aim of this study was to investigate whether intravenous immunoglobulin (IVIG) can prevent sepsis in premature newborn infants. The study group consisted of 80 preterm newborn infants, who were divided into two groups: 40 preterm newborns received IVIG prophylactically (group A) and the control group (group B, n = 40) did not receive IVIG. IVIG was given at a dose of 500 mg/kg to infants. weighing greater than 1500 g, and 700 mg/kg to those weighing less than 1500 g at birth on days one, two and eight of life.

By two, eight and 12 days of age, the treatment group had significantly greater IgG concentrations than the control group. Mortality was 7.5 percent (3/40) in group A and 27.5 percent (11/40) in group B ($p < 0.01$). Bacteremia was determined in three blood cultures in group A and eight in group B, particularly S.aureus and S.enteritis.
Key words: immunoglobulin, preterm infants, sepsis.

As a result of inadequate placental transport of maternal IgG, preterm neonates are more susceptible to severe infections than are term neonates[1]. In recent years, intravenously administered immunglobulin (IVIG) has been used for the prevention or treatment of neonatal sepsis[2-5].

The present study was conducted in Sivas, an eastern province of Turkey where socioeconomic conditions are unsatisfactory, and undernourished mothers have frequent pregnancies. The aim of this study was to investigate whether IVIG prevents sepsis in premature newborn infants.

Material and Methods

Eighty preterm newborn infants were included in this study and were divided into two groups on the basis of order of admission; the treatment group received IVIG (group A, n = 40) prophylactically and the control group did not receive IVIG (group B, n = 40).

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Conditions at birth that precluded enrollment of infants in the study included multiple life-threatening congenital anomalies, maternal infection and cardiopulmonary arrest. IVIG (Sandoglobulin R) was given at a dose of 500 mg/kg to infants weighing greater than 1500 g, and 700 mg/kg to those weighing less than 1500 g at birth on days one, two and eight of life. Blood samples were obtained to monitor IgG concentrations before every infusion of immunoglobulin and at 12 days of age. Serum IgG concentrations were identified by Behring Nor-Partigen (R) IgG HC radial immunodiffusion plates.

On the first day of life, the following laboratory eaminations were performed: cultures, of blood, stool, throat and the umbilicus; white blood cell count, band/total neutrophil ratio, platelet count and C-reactive protein. The cases having a positive blood culture were classified as "proved sepsis" and the others as "suspected sepsis". These examinations were repeated if sepsis was suspected[6].

Student's and Chi Square tests were used in the statistical analysis[7].

Results

Clinical features of the two groups are shown in Table I. The sex distribution, gestational age, weight, Apgar score and antibacterial treatment were identical in the two groups. Serum IgG concentrations are shown in Table II. The mean IgG concentrations on the first day of life were not significantly different between the two groups ($p > 0.01$). By two, eight and 12 days of age, the treatment group had significantly greater IgG concentrations than the control group. Sepsis developed in 12.5 percent (5/40) of cases in group A (3 proved, 2 suspected sepsis), and 40 percent (16/40) in group B (8 proved, 8 suspected) ($p < 0.02$, Table III). Bacteremia was determined in three blood cultures in group A and eight in group B, particularly S. aureus and S. enteritis (Table IV). The sepsis-related mortality rate was 7.5 percent (3/40) in group A and 27.5 percent (11/40) in group B ($p < 0.02$, Table V). The length of hospitalization was 8.32 ± 1.17 days in group B ($p < 0.05$).

No adverse effect related to IVIG administration in these neonates was observed.

Table I: Clinical Features in Treated and Control Infants

	Group A (IVIG)	Group B (No IVIG)	P
Gestational age	36.18 ± 0.17	35.58 ± 0.19	> 0.05
Birth weight (grams)	1.85 ± 0.07	1.67 ± 0.07	> 0.05
Mean Apgar score at 5 minutes	8.08 ± 0.17	7.83 ± 0.19	> 0.05
Sex (M/F)	24/16	18/22	
Use of antibiotic (+)	36 (90%)	37 (92.5%)	
Use of antibiotic (-)	4 (10%)	3 (7.5%)	

Table II: Serum IgG Concentrations

Days	Serum IgG (mg/dl) Group A (IVIG) n: 40 $\bar{X} \pm$ SD	Group B No (IVIG) n: 40 $\bar{X} \pm$ SD	P
1	775.54 ± 51.48	679.96 ± 49.88	> 0.01
2	1211.86 ± 75	742.31 ± 49.95	< 0.01
8	1075 ± 85.60	713.10 ± 45.11	< 0.01
12	1039.32 ± 37.10	744.51 ± 33.29	< 0.01

Table III: Sepsis in Each Group

	Group A (IVIG) n: 40	Group B (No IVIG) n: 40	X^2	P
Proved sepsis	3	8	3.84	p = 0.0501
Suspected sepsis	2	8	5.31	p = 0.020
Total sepsis	5	16	7.92	p = 0.0190

Table IV: Organisms Isolated from Blood the in Two Groups

Organism Isolated	Blood Culture Group A (IVIG)	Group B (No IVIG)
S.enteritis	2	–
S.aureus	–	3
E.coli	1	1
E.cloacea	–	2
Pseudomonas species	–	1
Corynobacterium species	–	1

Table V: Mortality Rate in Each Group

Group	Number	%
A (IVIG)	3	7.5
B (No IVIG)	11	27.5
$X^2 = 5.54$	$p < 0.02$	

Discussion

Infections are one of the most important problems of the newborn, particularly preterm infants. Preterm infants have a lack of IgG, because transplacental transport of IgG occurs predominantly in the latter half of the third trimester of pregnancy[1]. Besides, preterm infants may have certain defects in some steps of cellular and humoral immunity. For this reason, the incidence of sepsis is approximately 1/250 in preterms as compared to 1/1000 in term infants[8]. Therapy

with polivalent immunoglobulin concentrates has been used successfully. Sidiropoulos et al.[4,5] and Lindquists et al.[9] have shown a significant reduction in mortality using intravenous immunoglobulin for the treatment of sepsis.

Haque et al.[10] were the first investigators to use IVIG as a prophylactic agent. Their sepsis incidence was four percent (4/100) in newborns weighing less than 1500 g and 12 percent (6/50) in the control group. In a study by Chirico et al.[11], the incidence rates were seven percent (3/43) and 20 percent (8/40); Bussel et al.[12] found rates of 15 percent (9/61) and 25 percent (16/65), respectively.

In our study, the sepsis incidence in newborns was 12.5 percent (5/40) in preterm infants given IVIG, and 40 percent (16/40) among preterm newborn controls.

Clapp et al.[13] observed that no case of sepsis occurred in a study of 56 preterm infants administered IVIG compared with the control group, who had an incidence of 12 percent. The rate found by Baker[14] (46%) in controls is close to our result (40%), but Baker[14] found the sepsis incidence to be 34 percent with IVIG administration.

There have been other studies showing that the incidence of sepsis did not change when IVIG was administered[15]. Conway et al.[16] put forth that IVIG administered at a dose of 200 mg/kg might be insufficient for prophylaxis. The insufficiency of prophylaxis in the Weisman et al.'s[17] study may be due to the one-dose application of IVIG.

Kyllonen et al[18] stated that establishment of the dosage needed to reach target (700 mg/dl) levels would be useful. Our data demonstrated a reduced incidence of bacterial infection in the IVIG-treated group maintained at the serum IgG concentration of 700 mg/dl and greater (Table II). This is in accordance with Kyllonen's study.

Most of the studies show that IVIG administered in appropriate dosages to preterm and low-birth-weight babies is useful in preventing the occurrence of sepsis. In our study we showed a significant difference in the sepsis and mortality rates between the group treated with immunoglobulin (group A) and the group that remained untreated (Tables III-V). This finding corroborates that of previous studies.

The role of antibiotics in infections is undoubtedly important. In our study antibiotics were used in both group A + B, in 36 and 37 patients, respectively. The administration of antibiotics with IVIG was shown to lower the sepsis and mortality rates. In our study, microorganisms were detected in the blood culture of three patients in group A and eight patients in group B. Of the gram-positives, Staphylococcus aureus was predominant among the gram-positives, and the Salmonella species among the gram-negatives. Another important point is the short length of the hospital stay when IVIG was administered ($p < 0.05$).

We conclude that IVIG replacement therapy at an optimum dosage and longer intervals is both safe and effective for the prophylaxis of infection in high-risk, preterm, very-low-birth-weight infants with low levels of IgG.

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