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A STUDY ON ROLE OF IMMUNOTHERAPY (IVIG) IN THE TREATMENT OF NEONATAL SEPSIS IN A TERTIARY CARE CENTRE IN EASTERN BIHAR

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ABSTRACT

INTRODUCTION: Neonatal sepsis is a clinical syndrome characterised by systemic signs of infection accompanied by bacteraemia in the first month of life. Neonatal sepsis is a major cause of death and complications despite antibiotic treatment. Effective adjunctive treatments are needed. Newborn infants are relatively deficient in endogenous immunoglobulin.

OBJECTIVES: The present study was conducted to evaluate the effect of intravenous immunoglobulin (IVIG) in neonatal sepsis in preterm babies.

METHODS: The present study was conducted in the NICU of Jawahar Lal Nehru Medical College And Hospital, Bhagalpur, Bihar in which 100 newborn were enrolled for the study from February 2018 to January 2019. We used a dosage regimen of 1g/kg/day of IVIG. In this study we had 100 patients with documented sepsis; 50 of them received antibiotics (controls) and 50 of them received antibiotic and IVIG as adjuvant therapy. Finally we compared the outcomes of both groups.

RESULTS: In the present study, all septic newborns had positive blood cultures. The most common cause of sepsis in our study was Klebsiella (56% of control and 36% of case groups). In both groups we found 62% early onset sepsis. There was no statistically significant difference between mortality rate in two groups (52% VS 48% of case and control, P>0.05).

CONCLUSION: In our study it was found that there was no significant decrease in mortality rate with IVIG therapy in neonatal sepsis.

KEYWORDS : Intravenous Immunoglobulin (IVIG), Neonate, Preterm, Sepsis.

INTRODUCTION:

Neonatal sepsis is a clinical syndrome characterised by systemic signs of infection accompanied by bacteraemia in the first month of life.[1] In neonates, maternal, environmental and host factors determine the risk of sepsis on exposure to a pathogen. As the early signs may be nonspecific, a high degree of suspicion and some overtreatment is necessary to reduce its mortality and morbidity.

Neonatal infection and inflammation are associated with serious complications, including brain damage and disability, particularly among preterm infants.[2-5] Polyvalent IgG immune globulin may help to prevent or treat infection, particularly in preterm infants, who have low serum IgG levels. Possible immunomodulatory mechanisms include enhancement of opsonic activity, complement activation, antibody-dependent cytotoxicity, improvement in neutrophil chemiluminescence, and down-regulation of inflammatory cytokines.

Despite the advances in neonatal care, neonatal sepsis remains a major cause of mortality and morbidity in the newborn and 1.6 million neonates die every year from infection.[6-9] IgM is not trans-placental transferred and maternal IgG transfer starts around 30 weeks of gestation to reach maternal levels at term.[10] Hence the preterm infant is antibody deficient and this immune deficient state is worsened in sepsis.[11] The aim of treatment in severe infection is to kill the pathogens with antibiotics, control the hemodynamic impairment and organ dysfunction.[12] Recently, the International Sepsis Campaign published evidence-based guidelines for the treatment of sepsis. They indicated therapeutic modalities which are effective and which are not. The guidelines state that polyclonal IVIG therapy has been reported to reduce mortality rates in sepsis and are a promising therapeutic tool but asserted that there is insufficient evidence to suggest a robust conclusion of benefit.[12] The exact mode of action of IVIG is not clearly understood.[10] Commercially available polyclonal (IVIG) preparations contain over 96% IgG, containing a broad spectrum of opsonic and neutralizing antibodies aimed at a variety of organisms.[13] The World Health Organization has set minimum standards required of commercially available IVIG preparations. They include a minimal plasma donor pool of at least 1000.[10] Infused IVIG has a half-life of about 7 to 14 days in the newborn infant.[9] IVIG has the ability to neutralize bacterial toxins, modulate the production of pro and anti-inflammatory cytokines, chemokines and expression of adhesion molecules.[13-15].

Recently however, El-Nawawy et al have shown significant reduction in mortality, length of stay in intensive care in infants with sepsis syndrome treated with IVIG.[16] Alejandria suggested that IVIG lowers mortality in severe sepsis in adults.[17] Intravenous immunoglobulin has been used to treat and prevent neonatal sepsis since 1980 but its use still remains controversial.[18-19].

Though IVIG was first used in neonatal sepsis over a quarter of a century ago many clinicians still view IVIG therapy as either experimental or not evidence-based.

To improve the outcome from neonatal sepsis we will need not only to kill the pathogen but also modulate the immune system. Based on the evidence, immunomodulation with intravenous immunoglobulin in the management of neonatal sepsis is worth serious consideration. Hence this study was designed to evaluation the effect of intravenous immunoglobulin (IVIG) in neonatal sepsis.

MATERIAL AND METHODS:

This randomized clinical trial single blind study was done at the NICU of Jawahar Lal Nehru Medical College and Hospital, Bhagalpur, Bihar from February 2018 to January 2019. Sample size was determined with 95% confidence interval in 100 patients. There were 50 patients in case group and 50 patients in the control group. The study group was prescribed IVIG plus antibiotics and only antibiotics in controls. We used a single dosage regimen of 1g/ kg/day. Data were collected with a questionnaire and a check list. Infants with gestational age less than 37 weeks, birth weight less than 2500g, with sepsis diagnosis (positive blood culture) and hospitalized at the NICU were included in this study.

Exclusion criteria were congenital malformation, IUGR/ SGA, CPR upon delivery, low APGAR (<5), sever asphyxia, intraventricular hemorrhage, necrotizing enterocolitis, and neonates from addicted mothers. Finally data was analyzed with SPSS11.5 and chi-square tests.

RESULTS:

From February 2018 to January 2019, 100 patients were (50 in study and 50 in controls) with no gender differences (male 50%, female 50%) of neonates were enrolled in the present study. In case group there was no significant difference between 2 groups (p=0.25). There was no significant difference in gestational age between 2 groups (p=0.999, **Table 1**).

Table 1. Age of Sepsis onset.

Days	Control Group		Case Group		Total	
	No.	%	No.	%	No.	%
0-7 Days	36	72%	36	72%	72	72%
8-28 Days	14	28%	14	28%	28	28%
Total	50	100%	50	100%	100	100%
Chi-Square: X2 = 0.0			df = 1		P = 0.999	(NS)

The birth weight of the study group was 1350g with a standard deviation of 12 g and control group neonates were 1520 g with a standard deviation of 300 g. The mean gestational age of the babies was 32.90 ± 1.60 weeks in study group and 31.8 ± 2.3 weeks in controls. The mean age on admission was 6.2 ± 4.1 days and 5.3 ± 3.2 days in the study and control groups respectively. There was no significant difference between the groups in birth weight, gestational age or age (P>0.05). There was no significant difference between two groups in leucocyte count (P=0.812), neutrophil count (P=0.371), platelet count (P=0.400) or CRP (p=0.040). Neutropenia was present in 12.5% of control and 0 in the study group.

The predominant organisms causing neonatal sepsis in our NICU were Klebsiella (56% of control vs. 36% of case groups) then E.Coli (12% vs. 4%) and Acinetobacter (12% vs. 4%). Finally there was no statistically significant difference between mortality rates in both groups (P=0.999, **Table 2**).

Table 2. Mortality Rate

Mortality	Control Group		Case Group		Total	
	No.	%	No.	%	No.	%
Mortality Rate	24	48%	26	52%	50	50%
Total	50	100%	50	100%	100	100%
Chi-square : X2 = 0.0			df = 1		P = 0.999	(NS)

DISCUSSION:

In the present study, we did not find significant decrease in mortality in those who received IVIG in addition to the standard treatment (52% mortality rate in case group versus 48% in controls). There was no statistically significant difference in gestational age, birth weight and early or late onset sepsis. This is in view of the fact that not only is the outcome unaltered but also the mean duration of hospital stay was similar in the (IVIG) and control groups. El-Nawawy et al have shown significant reduction in mortality, length of stay in intensive care and complications in infants with sepsis syndrome treated with (IVIG). [16]

Alejandria suggested that IVIG lowers mortality in severe sepsis in adults.[17] Intravenous immunoglobulin has been used to treat and prevent neonatal sepsis since 1980 but its use still remains controversial.[18-19] Though (IVIG) was first used in neonatal sepsis over a quarter of a century ago many clinicians still view (IVIG) therapy as either experimental or not evidence-based.[17,21,22] Six studies (n = 318) which reported mortality showed statistically significant reduction in infants with suspected sepsis given IVIG (RR 0.63, 95% CI – 0.40-1.00).[23] Treatment with (IVIG) in seven trials (n=262) of cases of subsequently proven infection resulted in a statistically significant reduction in mortality following IVIG therapy (RR 0.55, 95% CI – 0.31- 0.98, NNT 11).(18-20).

Mathur et al showed a significant decrease in mortality in preterm neonates.[12] Although the number of studies are few and the total number of patients studied small but all the studies reviewed clearly show that the use of (IVIG) reduces mortality from neonatal sepsis significantly.[10] Thus, (IVIG) as adjuvant therapy offers a significant advantage over conventional therapy in sepsis. But Friedman et al showed no statistically significant difference.[11] A multicentre placebo controlled trial by Weisman et al showed significant decrease in mortality in the 1st 7 days, while the survival at 56 days had not improved significantly.[17] And In our study, we did not find any significant decrease in mortality in (IVIG) group.

In this study we concluded that there is no role of intravenous immunoglobulin (single dose not multiple dose) in the treatment of definite neonatal sepsis. We suggest, a larger sample size study, with multiple dose of (IVIG), in preterm septic newborns, to affirm the role of IVIG. Finally on the basis of the present study we can recommend that single dose IVIG therapy in preterm infants with positive blood culture is not useful in the management of neonatal sepsis in preterm infants.

CONCLUSION:

From the present study it was concluded that there is no role of intravenous immunoglobulin (single dose) in the treatment of neonatal sepsis; but we suggest, a larger study sample, with multiple dose therapy, in preterm septic newborns, to affirm the role of intravenous immunoglobulin (IVIG) in the management of neonatal sepsis.

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