Section: Paediatrics

Original Research Article

B ROLE OF INTRAVENOUS IMMUNOGLOBULIN AS AN ADJUVANT IN THE TREATMENT OF NEONATAL SEPSIS

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Abstract

Background: Neonatal sepsis is a primary cause of neonatal mortality and is an urgent global health concern. Neonates, especially preterm neonates are immune-incompetent and at increased risk of sepsis. In this study, we have seen if there is an improvement in the outcome of neonatal sepsis with the use of IVIg in conjunction with antibiotics as compared to using only antibiotics. **Materials and Methods:** This retrospective, observational study was conducted in a NICU in a tertiary care centre. The neonates with clinically suspected sepsis or proven sepsis were enrolled in the study after applying the inclusion and exclusion criteria. The neonates that were treated with Intravenous immunoglobulin (IVIg) with antibiotics were labelled as Group A. Group B was treated with antibiotics standard treatment protocol antibiotics. All the relevant data and outcome parameters were recorded and analyzed using appropriate statistical analysis. **Result:** The mean duration of NICU stay in Group B was 24.4±8.09 days and in Group A was 17.77±6.97 days. The difference between the two groups was found to be statistically significant (t=3.403, p=0.001). Mortality in the group treated with Intravenous immunoglobulin was 30% compared to 70% in Group B. Mortality rate was lower in Group A with a significant statistical difference. **Conclusion:** Intravenous immunoglobulin has an adjunctive role along with antimicrobial agents, to reduce mortality in Neonatal sepsis.

INTRODUCTION

Neonatal sepsis is an invasive infection, usually bacterial, and often occurs during the neonatal period (0–28 days).[1] Out of the three million annual neonatal sepsis cases occurring globally (2202/ 1,00,000 live births), India has the highest incidence of clinical sepsis (17,000/ 1,00,000 live births).[2] Neonatal sepsis is a primary cause of neonatal mortality and is an urgent global health concern, especially in low and middle-income countries including India.[3] Neonates, especially preterm neonates are immune-incompetent, they have a quantitative and qualitative deficiency in their humoral immunity, as the transfer of maternal antibodies to the fetus begins only after 32 weeks of gestation, and synthesis of endogenous immunoglobulin begins 24 weeks after birth.[4,5] They have a compromised innate immune system, due to immature epithelial barriers. They need invasive interventions, like vascular access/endotracheal intubation. This increases the risk of neonatal sepsis further.[1] Infants born before 32 weeks of gestation have cord blood concentrations of immunoglobulin less than 50% of those found in full-term babies. Additionally, very preterm babies have low complement factors, opsonic activity, and polymorphonuclear chemotaxis and are liable to exhaust this storage pool.[5,6] Intravenous antibiotic therapy is the mainstay of treatment of neonatal sepsis. As an increasing number of bacteria have developed resistance to antibiotics, hence effective adjuvant strategies are needed.

Administration of Intravenous immunoglobulin gives immediate high levels of antibodies, which should give a therapeutic benefit. Immunoglobulin can bind to cell surface receptors, provide opsonic activity, activate complement, prevent cytotoxicity, downregulate inflammatory cytokines, and improve neutrophilic chemo-luminescence.[5] Theoretically, neonatal sepsis-related morbidity, mortality, and adverse effects of infection, should be reduced by administration of intravenous immunoglobulin, in addition to receiving antibiotics. Three Cochrane reviews including 6000 neonates suggest that non-specific, polyclonal, intravenous immunoglobulin is safe, and reduced sepsis by 15% when used as prophylaxis. It has been suggested that intravenous immunoglobulin if used in the acute treatment of neonatal sepsis should reduce mortality by 45%.[7-11] Prophylactic administration of IVIg in neonatal sepsis had been studied in many Randomized

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controlled trials and has shown a significant reduction in infections,[11] However, the outcome of immunoglobulin in suspected sepsis as an adjuvant to standard treatment has been less studied.[5,8,9] The trials have been small and varied in quality. In this study, we have seen if there is an improvement in the outcome of neonatal sepsis with the use of IVIg in conjunction with antibiotics as compared to using only antibiotics.

MATERIALS AND METHODS

This study was a retrospective, observational study conducted in a Neonatal intensive care unit in a tertiary care center in the duration of July 2022 to December 2022.

Inclusion criteria

All Neonates (<28 days) admitted to the Intensive care unit with

1. Clinical signs of sepsis – apnoea/mottling/sclerema/temperature instability/feed intolerance/hemodynamic instability/respiratory distress
2. Positive sepsis screen – TLC <5000 cells/cumm / TLC >20000 cells/cumm / Band PMN>0.2 / ANC <1800 cells/cumm / CRP>1 mg/dl / micro ESR >10mmhr / platelet count <50000 cells/cumm
3. Culture-positive sepsis – bacterial or fungal culture positive of any sterile body fluid
4. Radiological evidence of pneumonia
5. Receiving antibiotics

Exclusion criteria

1. Primary immunodeficiency – suspected or proven
2. Rh incompatibility/HDN
3. TORCH infection in the mother
4. Multisystem inflammatory syndrome in Neonate
5. IVIg is contra-indicated
6. Parents or guardians not willing to enroll

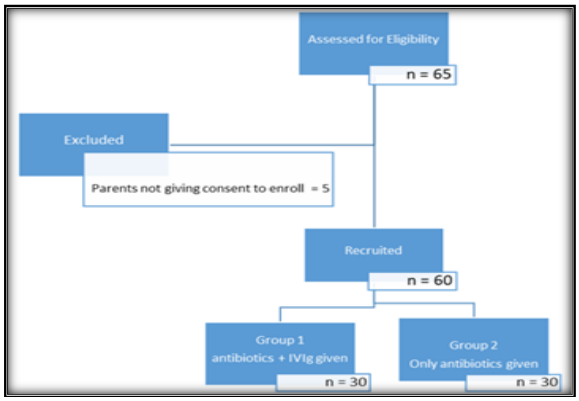

Figure 1: Study design

Procedure

The neonates with clinically suspected sepsis or proven sepsis over the period of six months were enrolled in the study. As elaborated in Figure 1, the neonates that were treated with 5% Intravenous immunoglobulin (IVIg) were labeled as Group A. They had received 5% IVIg, 1 gm/kg/dose, two doses over 48 hours along with the standard treatment protocol. Group B was treated with antibiotics standard treatment protocol. Neonates in both groups otherwise received the same general care. All the management decisions were taken as per the opinion of the senior Paediatrician. No special investigations or delay in discharge were done for this study.

All the relevant data, like age, sex, the indication of admission, the treatment received, lab parameters and outcome parameters were recorded in the case record sheet prepared by the researcher beforehand. The outcome parameters recorded were; the number of days of hospital stay, immediate outcome, and associated complications at discharge. Patients were discharged when vitals were stable, no antibiotics were necessary and oral feeds were established.

This data was filled in the Excel sheet. The collected data was subjected to analysis by appropriate statistical tests.

RESULTS

A total of 60 patients were enrolled, 30 in Group A and 30 in Group B. 11 (36.6%) females and 19 (63.3%) males were included in each group. [Table 1]

In Group A, 20% of patients were full-term, and 80% of neonates were premature. While in Group B, 36.6% of neonates were full term and 63.3% of neonates were preterm. In both groups, 13.3% of neonates had birth weight above 2.5 kg. In Group A, 33.3 % of neonates had birth weights between 1.5 kg to 2.5 kg and 56.6 % had birth weights between 1 kg to 1.5 kg. In Group B, 63.3 % of neonates had birth weight between 1.5 kg to 2.5 kg and 23.3 % of neonates had birth weight between 1 kg to 1.5 kg. There was no significant difference in both groups with respect to sex, maternal high-risk factors, age at admission, or birth weight. [Table 2]

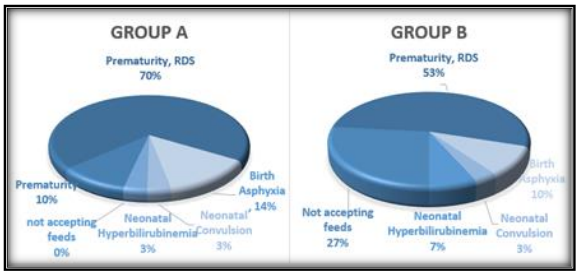

Figure 2: Indication of admission

The most common indication of admission was prematurity and respiratory distress (60%), not accepting feeds and feed intolerance (13.3%), birth asphyxia (11.6%), neonatal hyperbilirubinemia (5%), and convulsion (3.3%). Similar presentations were seen in Salihoglu et al,[12] and Ahmed et al,[4] However, the neonates admitted for prematurity had a significantly better outcome with Intravenous immunoglobulin as an adjuvant.

In Group A, 76.6% of neonates had features of shock, 70% of neonates required ventilator support, 60% had altered aspirate, 50% had hypoglycemia, 50% developed sclerema, 40% had poor activity, 26.6%

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had feed intolerance. In Group B 53.3% of neonates required ventilator support, 46.6 % were in shock, 43.3% had poor activity, 36.6% had altered aspirate, 36.6% had hypoglycemia, 20% developed sclerema, and 20% had feed intolerance. Neonates presenting with features of shock and sclerema showed a significant difference between outcome in the two groups. 61.6 % of neonates presented with Early onset sepsis and 38.3% of neonates presented with late-onset sepsis. There was no significant difference between the two groups with respect to age at the time of presentation. [Table 3]

Leucocytosis was seen in 3.33% of neonates in Group A and 26% of neonates in Group B, and Leucopenia was seen in 3.33% of Group A and 43.3% in Group B. It had no statistical significance in the outcome in both group. However, Absolute neutrophil count was seen to have a significant impact on the outcome in both groups. Thrombocytopenia (<1 lakh) was seen in 20% of neonates and 53.3% of neonates in Group B had thrombocytopenia. Thrombocytopenia was highly significant in the outcome of the study. [Table 4]

In Group A and Group B, 66.6% and 70% of neonates had positive CRP, but there was no difference in outcome in both groups based on CRP. In Group A, 63.3% of neonates had sterile cultures, whereas 56.6% of neonates in Group B had sterile cultures. Commonly noted organisms were Coagulase-negative Staphylococcus, Klebsiella pneumonia, Escherichia Coli, and Staphylococcus aureus. The growth of organisms and the species of organisms on culture showed no impact on outcome in either group. CSF analysis was done in only a third of the patients in both groups. 10% of neonates in Group A and 13% of neonates in Group B showed a picture of bacterial meningitis. [Table 5]

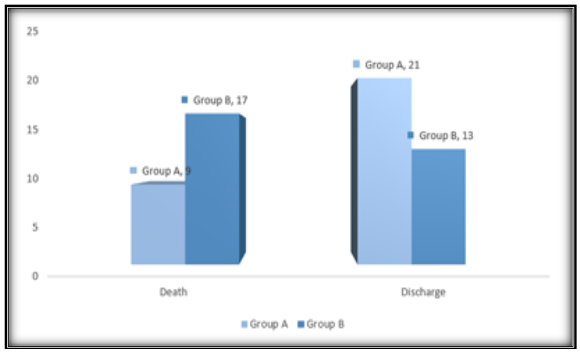

Figure 3: Outcome parameters

The mean duration of NICU stay in Group B was 24.4±8.09 days and in Group A was 17.77±6.97 days. The difference between the two groups was found to be statistically significant (t=3.403, p=0.001). Mortality in the group treated with Intravenous immunoglobulin was 30% compared to 70% in Group B. Mortality rate was lower in Group A with a significant statistical difference (c ²= 4.344, p<0.05).

Table 1: Baseline Characteristics of Neonates Enrolled (n=60)

	Group A	Group B
Female	11	11
Male	19	19
Full term	6	11
Preterm	24	19
Birth weight (mean) 1.0 – 1.5 kg	1700±486 gm 17	1950±563 gm 7
1.5 – 2.5 kg	10	19
>2.5 kg	4	4

Table 2: Indication of Admission (n=60)

Indication of admission	Group A	Group B
Birth Asphyxia	4	3
Neonatal Convulsion	1	1
Neonatal Hyperbilirubinemia	1	2
Not accepting feeds	0	8
Prematurity	3	0
Prematurity, RDS	21	16

Table 3: Condition of patients at the time of admission (n=60)

	Group A	Group B	Chi-square test (p-value)
Shock			5.711 (<0.05)
Present	23	14	
Absent	7	16	
Activity			0.069 (>0.05)
Fair	18	17	
Poor	12	13	
Sclerema			5.934 (<0.05)
Present	15	6	
Absent	15	24	
Altered Aspirate			3.270 (>0.05)
Present	18	11	
Absent	12	19	
Feed Intolerence			0.376 (>0.05)

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Yes	8	6	
No	22	24	
Hypoglycaemia			1.086 (>0.05)
Yes	15	11	
No	15	19	
Ventilator support			1.73 (>0.05)
Yes	21	16	
No	16	14	

Table 4: Laboratory parameters on admission (n=60)

Parameter	Study group	Mean	Std. Deviation	Independent t-test	p-value	Significance
Total Leucocyte Count	Group A	7327.67	8041.26	-1.372	0.175	Not Significant
	Group B	10655.33	10576.76			
Absolute Neutrophil Count	Group A	3658.23	4587.94	-2.126	0.038	Significant
	Group B	7419.17	8535.50			
Platelet count	Group A	51700.00	27214.54	-3.084	0.003	Highly Significant
	Group B	112833.33	105117.37			

Table 5: Sepsis screen of the study population (n=60)

	Group A	Group B	Chi-square (p-value)
C Reactive Protein			0.77 (>0.05)
Positive	20	21	
Negative	10	9	
Blood culture			7.11 (>0.05)
Positive	11	13	
Sterile	19	17	
Cerebrospinal fluid analysis			1.056 (>0.05)
Meningitis	3	4	
No meningitis	7	4	
Not performed	20	22	

Table 6: Primary Study Outcome (n=60)

	Group A	Group B	p-value
NICU Stay	17.77±6.97 days	22.4±8.09 days	0.001
Outcome			<0.05
Discharge	21 (70%)	13 (43.33%)	
Death	9 (30%)	17 (56.66%)	

DISCUSSION

In this study, both groups were comparable for both age and sex, birth weight, and gestational age. The demographic showed a higher incidence of sepsis in preterm babies. The patients' clinical presentation was similar to that in similar studies or described in the standard textbook.[6,12]

In the present study, NICU stay in Group A was (17.77±6.97 days) as opposed to (24.4 ±8.09 days) in Group B. This association was statistically significant (p=0.001). Mishra K et al, 2020,[14] a randomized study in India; Li Yuhnag et al. 2019,[15] showed no significant difference in the hospital stay in the group treated with IVIg as opposed to the one treated with a placebo. Awais Mirza et al., 2017,[16] Lassiter HA,[17] SS Ahmed,[4] Kinney et al,[18] reported that administration of IVIg was associated with diminished length of hospitalization.

Sidiroplus 1981,[19] was the first to report the use of IVIg to treat established bacterial sepsis in neonates. In this study, the incidence of death was 27% in the study group and 10% in the treatment group (p=0.016). IVIg appeared to be most effective in very low birth weight neonates with sepsis. In the current study, mortality in the group treated with Intravenous immunoglobulin was 30%, significantly lower than the 70% in Group B. (c^2= 4.344, p<0.05).

Haque KN et al, 2004,[20] in their two studies concluded that the mortality from sepsis is significantly lower in the IVIg-treated group (p<0.001). SS Ahmed 2006,[3] showed a lower mortality rate in the group treated with IVIg (13.3%) in comparison to the study group (33.3%), although not statistically significant, the tendency shows a reduction in the mortality rate in the IVIG-treated group.

There is good preliminary evidence that IVIg therapy may reduce mortality in severe sepsis as an adjuvant to antibiotic therapy, especially in the preterm neonate. However, the safety and long-term consequences of IVIg therapy need to be explored further.

CONCLUSION

Neonatal sepsis is a primary cause of neonatal mortality, despite the advent of antimicrobial therapy. Preterm neonates are especially prone to sepsis due to immature immunity and deficient immunoglobulins. Supplying deficient passive immunity in the form of Intravenous immunoglobulin has an adjunctive role along with

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antimicrobial agents, to reduce mortality in Neonatal sepsis.

Limitations

This study is restricted to a single center, and observational type. No segregation was done according to the gestational age of the neonates. This study has a limited sample size. A multicentric, interventional trial should be undertaken with a larger sample size. There was no data regarding the safety and long-term consequences of the administration of IVIg. This study did not do a follow-up of discharged patients and the long-term outcomes of IVIg therapy on morbidity and mortality. The long-term risks and benefits need to be studied further.

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