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OUTCOME ASSESSMENT OF INTRAVENOUS IMMUNOGLOBULIN THERAPY AS AN ADJUVANT IN TREATMENT OF NEONATAL SEPSIS, A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Despite effective antibiotics treatment, mortality due to neonatal sepsis remains high. Immunomodulatory therapy like intravenous immunoglobulin (IV Ig) has been used as an adjunct in an effort to decrease mortality from neonatal sepsis, as newborn infants, particularly those who are preterm and are deficient in IgG. The objective of this study was to assess the outcome of intravenous immunoglobulin therapy as an adjuvant in the treatment of neonatal sepsis. A total of 42 babies who were given IV Ig as an adjuvant along with antibiotics for proven neonatal sepsis formed the potential subjects. Clinical and hematological parameters were assessed following IV Ig administration. The total duration of Neonatal intensive care unit stay was noted. The source, dose, frequency and adverse effects, if any of IV Ig were noted. In our study, both male and female babies were equally affected. More than 90% of the babies were preterm and all the babies had low birth weight. The source of IV Ig was IgG, obtained from pooled human plasma. It was given at the dose of 0.5-0.9 g/kg. No adverse reaction following IV Ig was noted. Following IV Ig administration as an adjuvant in treatment of neonatal sepsis, the improvement in clinical and hematological parameters were better and quicker. The average duration of hospitalization was 6-8 days when IV Ig was given as an adjuvant. Thus duration of NICU stay was less when compared to being treated with antibiotics alone. Hence to conclude, IV Ig as an adjuvant along with antibiotics is a better strategy for both prophylactic as well as treatment of proven neonatal sepsis.

KEY WORDS: **Intravenous immunoglobulin, adjuvant, antibiotics, neonatal sepsis**

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INTRODUCTION

"One of the most common cause of neonatal deaths in our country is neonatal sepsis. Neonatal sepsis was a major cause of mortality and morbidity and has been implicated in the causation of perinatal brain damage and cerebral palsy, both in term and preterm infants.[1,2] The World Health Organization (WHO) estimates that 1 million deaths per year (10% of all under-five mortality) are due to neonatal sepsis and that 42% of these deaths were occur in the first week of life.[3] Worldwide, the incidence of neonatal sepsis is 6.6 per 1000 live births and 15.4 per 1000 very low birth weight babies.[4] The infant mortality rate of India is 47/1000 live births, Of which 70 % of deaths is in neonatal period with sepsis being one of the leading causes of death.[5] The early manifestations of neonatal sepsis are vague and ill-defined. Although blood culture is the gold standard for the diagnosis of sepsis, culture reports would be available only after 48-72 hours. Hence it is prudent to provide treatment for suspected neonatal sepsis with empirical antibiotics. [6] Although antibiotics are the mainstay of therapy, increasing numbers of bacteria were resistant to them. Effective adjunctive strategies are therefore needed.[7,8] Immunopharmacology is a recent upcoming branch of pharmacology that comprises of immunostimulants, immunosuppressants, immunomodulators, monoclonal antibodies and immunoglobulins. These group of agents have a wide diagnostic and therapeutic application in the current era in the field of cancer, cell biology, genetics and molecular research. [9] Immuno-modulatory therapy like intravenous immunoglobulin (IV Ig) has been used as an adjunct in an effort to decrease mortality from neonatal sepsis as newborn infants, particularly those who are very low birth weight or preterm are deficient in IgG.[10] Various trials have been published using IV Ig as therapy in neonatal sepsis.[11-13] These trials have been difficult to compare in view of the different doses, frequency, source of IV Ig and infecting organisms. They all have been conducted in centers from advanced countries where the organisms causing neonatal sepsis are different from our setting. Indian neonatal units report a predominance of Gram negative organisms like Klebsiella, Pseudomonas, etc. and Gram positive bacteria like Staphylococcus aureus.[14] The use of intravenous immunoglobulin (IV Ig) for the prevention and treatment of sepsis in neonates is appealing because of the relative immunodeficiency of the neonate and the desire to improve the relatively poor outcome even with optimal antimicrobial treatment. The effectiveness of IV Ig for these uses has been studied in numerous prospective as well as retrospective small and large trials that have had discordant conclusions.[15] This study aims at assessing the outcome after intravenous immunoglobulin administration as an adjuvant in treatment of neonatal sepsis.

MATERIALS AND METHODS

This study was done after obtaining the approval from Institutional Human Ethical Committee (IHEC) of Sri Balaji Vidyapeeth University, Puducherry. The study was carried out in collaboration with the Department of Paediatrics, Neonatology division, Mahatma Gandhi Medical College and Research Institute

Eligibility Criteria
Inclusion Criteria

- Newborn babies admitted in the neonatal intensive care unit and diagnosed to have sepsis who were treated with intravenous immunoglobulin formed the potential subjects.

Exclusion Criteria

- Neonates with major congenital malformations
- Neonates with surgical problems

Study Design

- Prospective, Descriptive, Observational open label study conducted at MGMC & RI

Procedure

This study was done from January 2011 till April 2012. During this period, Newborn babies admitted in the neonatal intensive care unit and diagnosed or suspected to have sepsis who

were treated with intravenous immunoglobulin and antibiotics were taken for study. A total of 42 babies admitted in NICU during the study period was given intravenous immunoglobulin for diagnosed sepsis. It included both early onset as well as late onset neonatal sepsis. Diagnosis of neonatal sepsis was made based on the clinical features and laboratory investigations. Poor cry and feed, lethargic activity, grunting, costal and sternal retractions, nasal flaring, tachypnea or irregular respiration, rales, decreased breath sounds were some of the common clinical features. Hypoglycemia, hyperglycemia, metabolic acidosis, jaundice and other metabolic signs if present were noted. Laboratory parameters included an abnormal total leukocyte count, abnormal total neutrophil (PMN) count, elevated immature PMN count and platelet count.

Role of intravenous immunoglobulin was assessed by the following parameters

- Clinical examination
- Duration of stay in NICU
- Hematological investigation

Clinical examination

Clinical assessment of the progress of the baby day by day was made by making a thorough physical examination.

Duration of stay in NICU

The total duration of stay from the date of admission till the discharge of the baby was noted.

Hematological investigations

Total count, Neutrophil count, Platelet count, C-reactive protein and blood C/S were done and the counts on successive days were assessed. The following parameters of intravenous immunoglobulin were assessed

- Source
- Dose
- Frequency
- Adverse reaction (if any)

Source of IV Ig

The source of the Ig- IgG
Brand name: Gamma IV (Bharat serum and vaccines) and
El-gam (Uphar Speciality Pharma)

Dose of IV Ig

Dose administered was 0.5-1 g/kg Ig depending on the weight of the baby

Frequency of IV Ig

The number of doses administered were noted

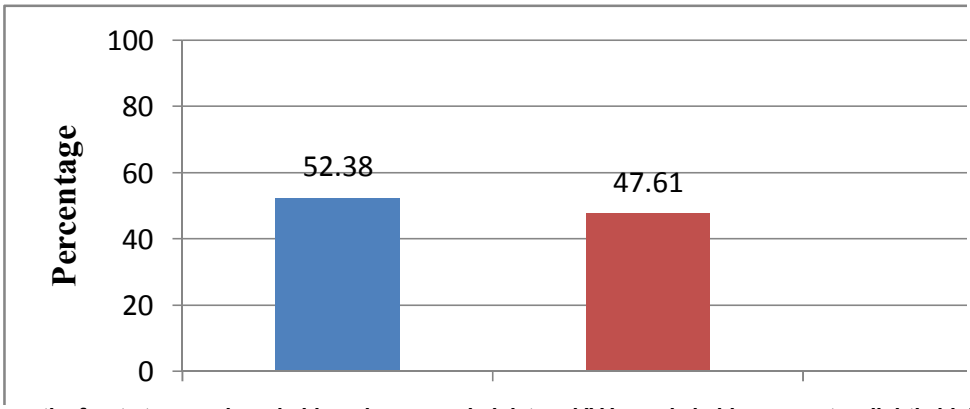
Adverse reaction

Adverse reaction if any was noted.

- Babies were followed till their discharge from NICU

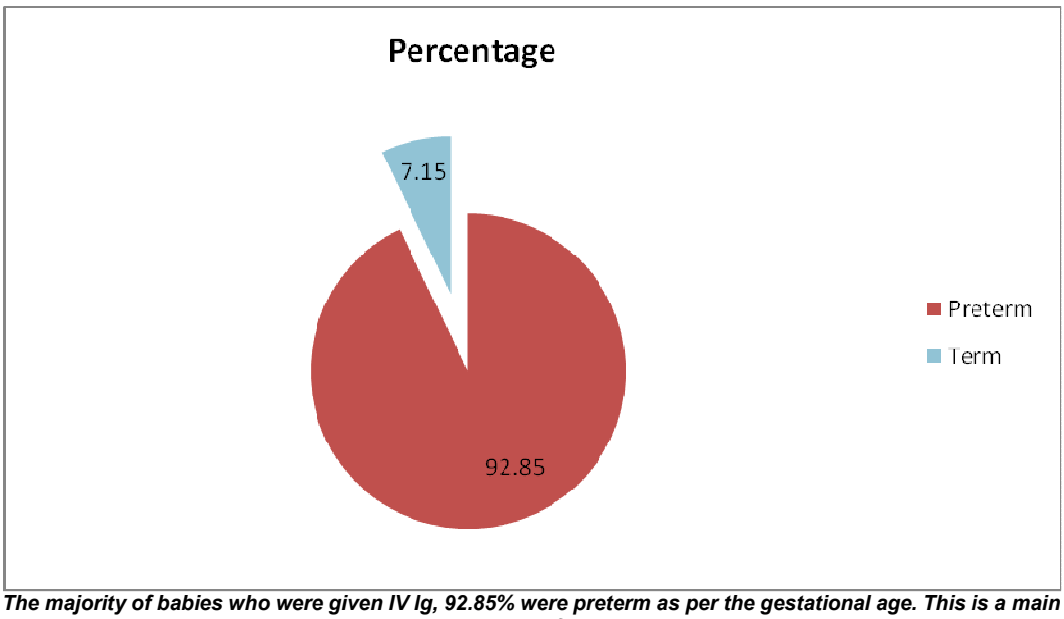
RESULTS

Figure 1
Gender distribution



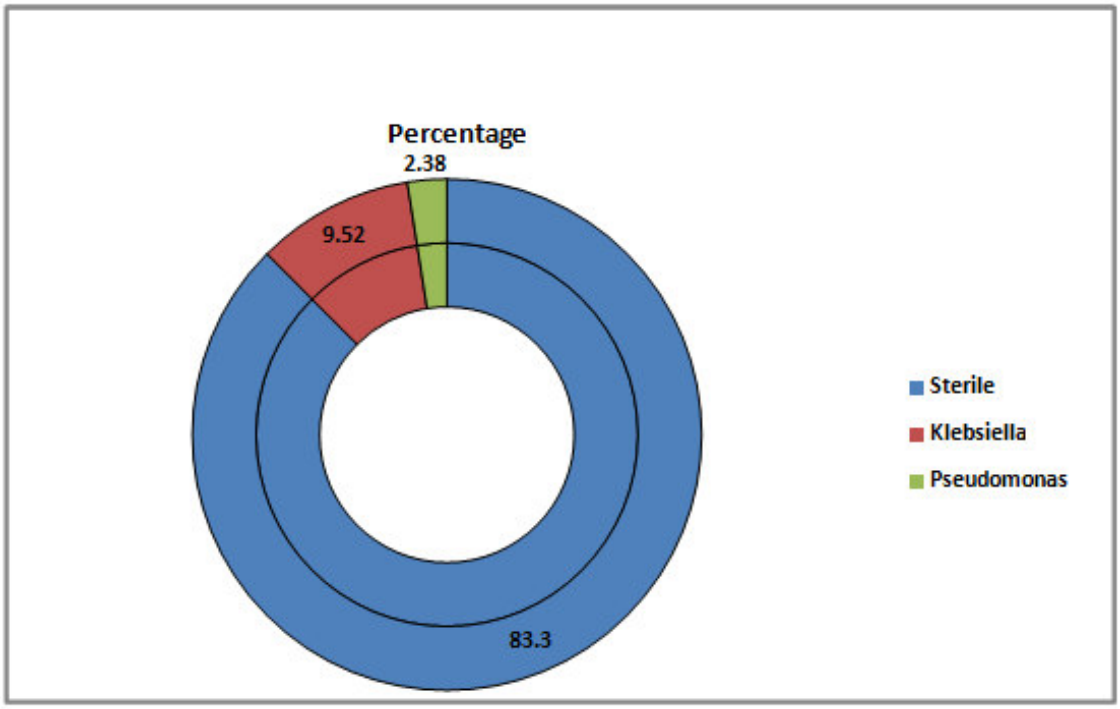
Among the fourty two newborn babies who were administered IV Ig, male babies were at a slightly higher Preponderance (52.38%) in ratio than female babies (47.61%) who were treated for neonatal sepsis.

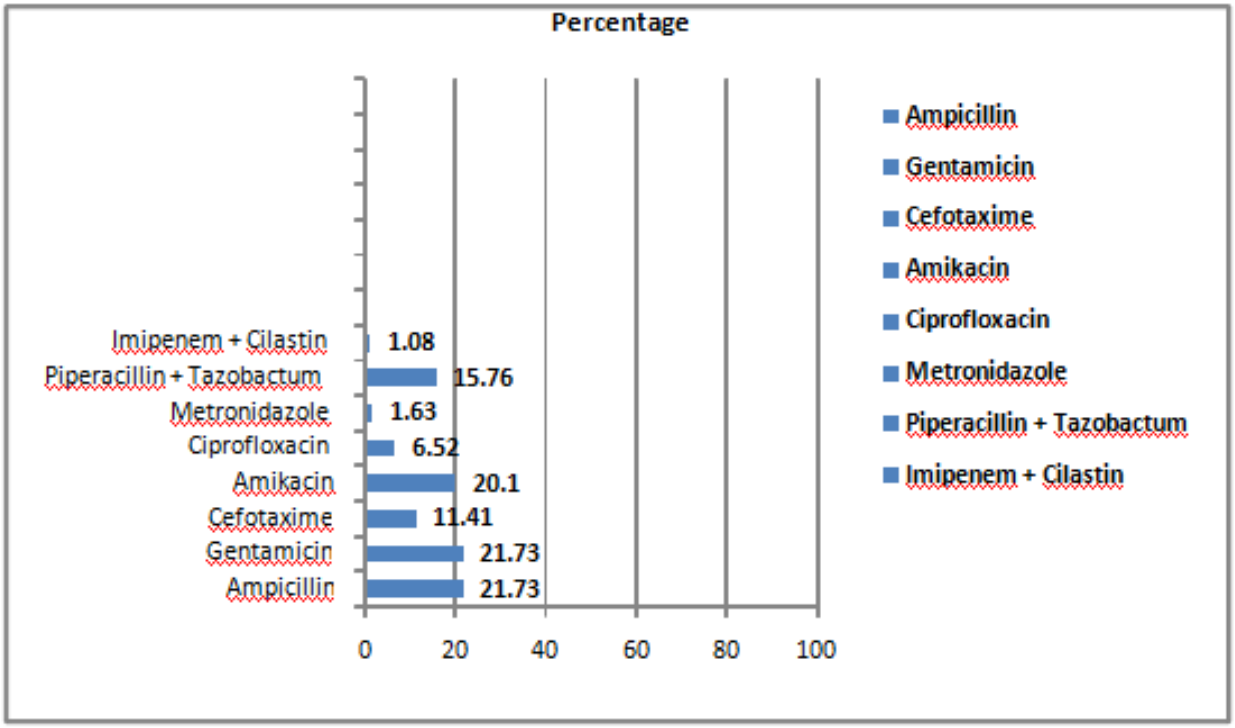
Figure 2
Gestational age



The majority of babies who were given IV Ig, 92.85% were preterm as per the gestational age. This is a main indicator that preterm babies are more prone for neonatal sepsis than the term babies.

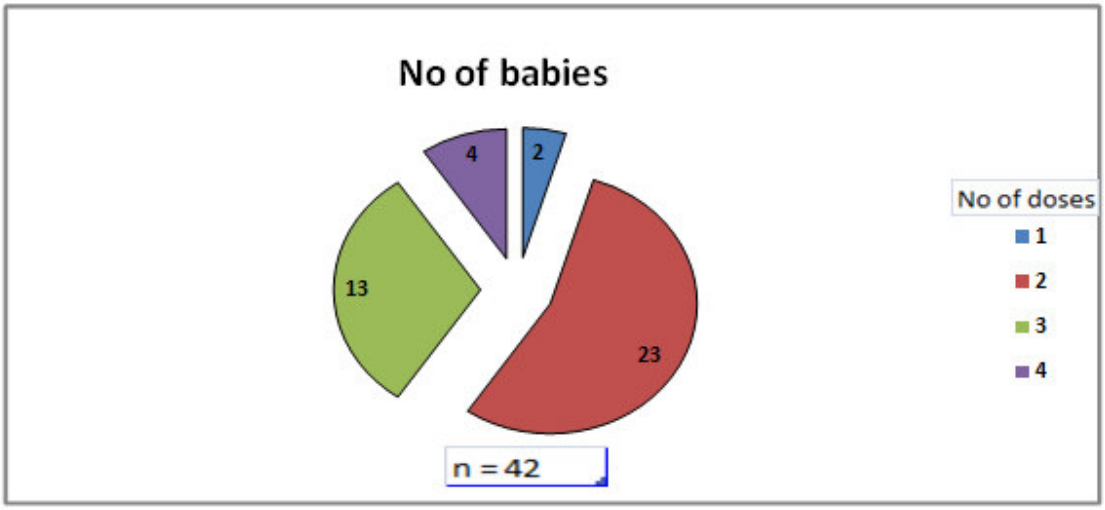
Figure 3
Blood Culture





Klebsiella was reported in 4 cases followed by Pseudomonas in 2 cases. But major portion of the isolate were sterile. The chief organisms were Klebsiella and pseudomonas in our neonatal intensive care unit during the study period.

Figure 5
Number of doses of IV Ig



The number of doses of IV Ig administered ranged from one to four. More than 50 % of the babies were given 2 doses of IV Ig based on the improvement in clinical features and laboratory parameters. No adverse reaction or adverse event was found following IV Ig administration.

Table 1
Neutropenia observed and improved after IV Ig therapy

Neutropenia observed	Neutropenia improved on successive days
n = 42	36 (85.71%)

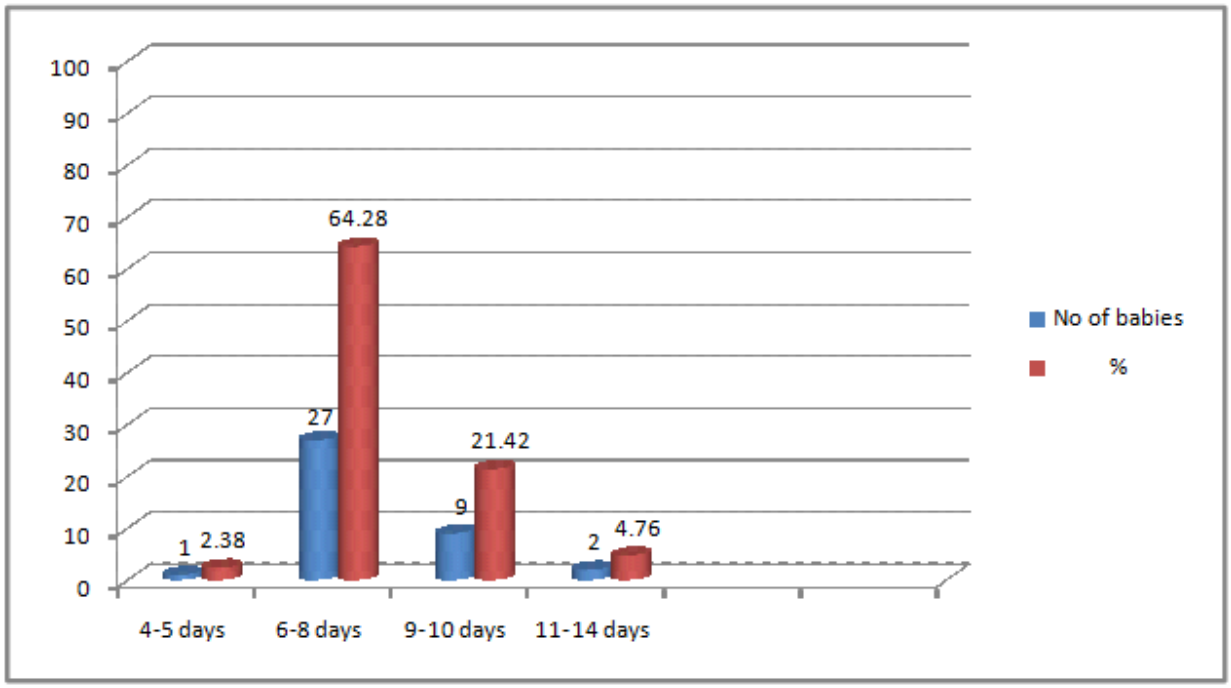
Decreased polymorphonuclear neutrophil count was present at day 1 of admission in all the babies. Following antibiotics and IV Ig administration, there was improvement in neutropenia in more than 85% of the babies.

Table 2
Platelet count observed and improved after IV Ig therapy

Platelet count observed	Thrombocytopenia observed	Thrombocytopenia improved
n = 42	32 (76.19%)	32 (100%)

All the babies showed improvement in platelet count after treatment with antibiotics and IV Ig. C-reactive protein was non reactive in all the babies. Once IV Ig was given as an adjuvant, there was a rapid improvement in both neutropenia and thrombocytopenia. This reduced the duration of NICU stay, which is illustrated in the following figure

Figure 6
Duration of NICU stay



The major number of babies (Nearly 65%) were in the NICU between 6 to 8 days following admission.

DISCUSSION

In this prospective observational study, 42 newborn babies who were administered IV Ig for probable or proven sepsis formed the potential subjects. In our study, both male and female babies were equally affected and babies which had late onset neonatal sepsis were predominantly male. This was similar to a study conducted by Remington et al. In a study conducted by Sidiropoulus et al, neonatal sepsis was much predominant in preterm babies and showed a significant reduction in mortality rate. In our study also neonatal sepsis rate was found more than 90 % in preterm and low birth weight babies. With reference to the blood culture and reported organisms, It is klebsiella and pseudomonas that was isolated in our neonatal intensive care unit during the study period. This was similar to a study conducted in Bangalore by Shenoi et al. The total number of antibiotics used in our NICU

during the study period was 8. Of the 184 prescriptions, Ampicillin and Gentamicin were the maximum with each 40 in number as they were started empirically. This was followed by Amikacin and Cefotaxime based on the progress of clinical features. Ciprofloxacin and metronidazole were also used depends on the culture and sensitivity report. The fixed dose combination of Piperacillin and Tazobactum was used in 29 babies ie for nearly 60% of the babies. Another fixed dose combination of Imipenem and Cilastin was given for 2 babies. In our present study, the source of IV Ig was IgG obtained from pooled human plasma. The branded formulations used were Gamma IV (Bharat serum and vaccines) and El-gam (Uphar Speciality Pharma) It was given at the dose of 0.5-0.9 g/kg similar to a study conducted by Werdan et al. The mean requirement of IV Ig in our study was 2 doses. No adverse reaction following IV Ig was noted. It was well tolerated by all the babies after administration. In our study the average duration of NICU stay was 6-8 days which was seen in nearly 65% of the babies. This showed that there was a lesser duration of stay in NICU when compared to being treated with antibiotics alone for neonatal sepsis. There was a good improvement in both the clinical progress as well as the hematological parameters after the introduction of IV Ig. Thus reducing the duration of NICU stay when compared to being treated with antibiotics alone. In India, only a very few studies were done on IV Ig in the treatment of neonatal sepsis. But interestingly, a Cochrane systematic review of reports of RCTs of IV Ig therapy for proven or suspected neonatal sepsis identified nine studies that reported outcomes for 318 infants with suspected infection and 262 infants with proven infection IV Ig therapy appeared to be safe and was associated with approximately 40% reduction in the risk of mortality for both suspected infection and proven sepsis. Overall, there was a reduction in deaths in NICU due to neonatal sepsis during our study period compared to the previous years. The usage of IV Ig also increased from last year to this year. In our NICU, IV Ig is being used for probable or proven sepsis when there is no improvement in the clinical progress and laboratory parameters after the initial antibiotics administration. But this cannot be done as a mandatory protocol, as different neonatal units have different antibiotic policies and neonatal sepsis management protocol. But in our study IV Ig as an adjuvant along with antibiotics proved to be an effective strategy in management of neonatal sepsis.

CONCLUSION

Following IV Ig administration as an adjuvant in the treatment of neonatal sepsis, the improvement in clinical and hematological parameters were better and quicker. Thus along with antibiotics, IV Ig reduced the duration of NICU stay. The average duration of hospitalization was 6-8 days. Moreover no adverse reaction or event was reported following IV Ig administration. The study of antibiotic utilization pattern showed that β lactam group of antibiotics, cephalosporins and aminoglycosides were used more in our NICU. Further, antibiotic resistance is a big challenge to the treating physicians and the usage of immunoglobulins in this context is a promising approach. Hence to conclude, IV Ig as an adjuvant along with antibiotics is a better strategy for both prophylactic as well as treatment of proven neonatal sepsis.

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