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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/13003
DOI URL: <http://dx.doi.org/10.21474/IJAR01/13003>



ISSN NO. 2320-5407

RESEARCH ARTICLE

A COMPARATIVE OBSERVATIONAL STUDY TO EVALUATE THE EFFECTIVENESS OF INTRAVENOUS IMMUNOGLOBULINS IN THE MANAGEMENT OF NEONATAL SEPSIS IN PRE- TERM AND TERM NEONATES

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Manuscript Info

Manuscript History

Received: 10 April 2021
Final Accepted: 14 May 2021
Published: June 2021

Abstract

Introduction: Neonatal sepsis is still one of the major causes of morbidity and mortality in neonates, effective adjunctive treatments such as addition of IVIG to standard antibiotic treatment is needed. Neonates conceived <32 weeks of gestation are immune deficient of immunoglobulins when compared to neonates conceived at full term.

Aims and Objectives: This study has been attempted to assess and compare the effectiveness of IVIG in addition with antibiotics to improve the therapeutic consequence of NNS in preterm and term neonates.

Materials and Methods: A prospective observational study was conducted, in which 80 neonates were enrolled. Both preterm and term neonates with sepsis were randomly assigned into study and control groups at neonatal intensive care unit, Owaisi Hospital & Research Centre, Hyderabad, India. Study-group was given IVIG in addition to standard treatment. The test group was treated only with the standard antibiotics.

Results: In our study, both the study and control-groups were practically identical based on baseline characteristics. The addition of IVIG as an adjunctive therapy is effective in management of NNS as the study group is found to have less duration of hospital stay when compared to that of control group and was statistically significant. The mortality rate was also found to be less in study group and the difference between the two groups is found to be statistically significant.

Conclusion: Low levels of immunoglobulins in preterm as well as in term neonate's results in increased morbidity and mortality in NNS. Use of IVIG along with the antibiotics and other supportive therapy can improve the outcomes such as hospital stay and mortality.

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Introduction:-

Neonatal septicemia is a type of infection, specifically refers to presence of bacterial blood stream infections, if occurring within first 2-3 days is referred to as early onset sepsis, lateonset sepsis develops after 3 days of birth.¹

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According to WHO estimates, there are about 5 million neonatal deaths a year, 98% occurring in developing countries.² Infection, prematurity, and birth asphyxia are the main causes. It is generally assumed that neonatal mortality in developing countries is under-reported by at least 20%.² According to recent data from National Neonatal Perinatal Database (NNPD) 2000, the incidence of neonatal sepsis has been reported to be 38 per 1000 intramural live births in tertiary care institutions.³ Premature infants have an increased incidence of sepsis, with a significantly higher occurrence in infants with a birth weight lower than 1500 g (11-22.7 per 1000 live births) than in infants born at 37 weeks or later (0.3-0.98 per 1000 live births). India has the highest incidence of clinical sepsis (17,000/ 1, 00,000 live births).⁴ The case fatality rate of sepsis among neonates ranges between 25 -65 % in India.

Sepsis screening study provides an extremely reliable index of neonatal sepsis and serves as useful guide for initiating antibiotic therapy. When at least two of the following are positive, it is considered as sepsis. Diagnosis tests include CRP levels (>6mg/L), High ESR (>10 mm 1st hour), Low Neutrophil count (<1800/mm³), Low Leukocyte count (<5000/mm³), High Immature to Total neutrophil ratio (>0.2) Culture positive (Blood, CSF, Urine) The pathogenesis of the neonate's predilection to infection are multifactorial. Obstetric factors, monitoring devices, and therapeutic procedures may trigger neonatal infections. Factors directly attributable to the infant, including deficiencies in the various arms of the immune system, play major roles in their predilection to infection. Neonates are viewed as immunocompromised in perspective of their moderately immature defense mechanism as they are relatively deficient in endogenous immunoglobulin (IgG).⁵

Globally, sepsis is still one of the major causes of morbidity and mortality in neonates, despite antibiotic treatment.⁶ Effective adjunctive treatments such as addition of IVIG to standard antibiotic treatment is needed.

Several studies have shown a lower risk in death in septic neonates given antibiotics plus IVIG, compared to neonate's given only antibiotics. Also neonates who are not responding to standard antibiotic treatment and supportive measures might be benefited by IVIG therapy. The additional benefit of decreasing the complications and decrease in the length of hospital stay indicates that the inclusion of IVIG should be considered apart of the routine therapy of neonatal sepsis.^{7,8}

Aims & Objectives:-

This study has been attempted to assess and compare the effectiveness of IVIG in addition with antibiotics to improve the therapeutic consequence of sepsis in preterm and term neonates

Methodology:-

It is a Prospective Observational study, was carried out for 6 months in Neonatal intensive care unit, Owaisi hospital & research centre, Hyderabad. Around 80 neonates (40 of control group and 40 of test group) was selected based on following criteria

Inclusion Criteria:

Preterm and full term (both the gender), Neonates diagnosed with sepsis with at least two positive sepsis screening tests (High CRP levels, High ESR, Low Neutrophil count, Low Leukocyte count, Culture positive (Blood, CSF, Urine). Early onset and late onset sepsis.

Exclusion Criteria:

Neonates >28 days of age, Had infections associated with toxoplasma, rubella, cytomegalovirus, and herpes simplex viruses (the TORCH complex), Neonates with any complications (other than sepsis), Recurrent sepsis and neonates who previously received IVIG.

Study approval:

The study has been carried out in the NICU, department of Pediatrics, Owaisi Hospital and Research Centre after getting the permission from the Institutional Review Board, Institutional Ethics Committee and the head of the department of Owaisi Hospital and Research Centre and Deccan College of Medical Sciences, Kanchanbagh, Hyderabad.

IRB NO: 2019/29/006

Procedure:

The study includes the comparison of standard antibiotics treatment vs antibiotics along with IVIG as adjunctive therapy. The patient's were diagnosed with sepsis based on CRP, CBP, blood culture and symptoms. The patients were randomly divided into two groups – test and control. Control groups include patients of sepsis treated with standard antibiotics. Test group was given IVIG along with the standard antibiotics for the treatment of sepsis. Then the patients were observed for their recovery from sepsis by taking lab tests like CRP and CBP. The above data will be used to assess the resolution of infection and the length of hospital stay.

Results:-

Total 80 patients were enrolled, 40 in control and 40 in test group. There were no gender differences (males 50% & females 50%) which are also evident from the test group (males 65%, females 35%) and control group (males 65% & females 35%). Average birth weight of neonates in study group 2.39 kg, and in control group it is 2.38 kg. Average birth weight of neonates in study group 2.39 kg, and in control group it is 2.38 kg. The average age of males was 8.72 days, were as for female's it was 8.45 days in control group, in test group, the average age of male was 7.25 days, were as for females it was 7.12 days.

There was no significant difference between the control group and test group in respect to gender, birth weight, gestational age, natal history (LSCS/NVD). The clinical profile of control and test group showed no significant differences (table 1). Blood culture revealed that 90% positive in control group and 92.5% positive in test group, showing klebsiella as the most common organism in both the group (45% & 47.5% for control and test respectively) (table 2). CRP was found 100% positive in both the groups.

Ig M, Ig A and Ig G levels were done only in the test group before and after the treatment with IVIG to see the changes in their levels, statistical t-test was done and statistically significant changes were found in their levels before and after the treatment (table 3). The mean hospital stay of control group was found to be 12.05 ± 5.43 days and of test group was 6.57 ± 2.10 days, the p value ≤ 0.05 indicates that the difference between the two groups is found to be statistically significant. Out of 80 patients enrolled in both the groups, 77 (96.25%) were treated and discharged, the mortality rate was 3.75% among 80 cases. No deaths occurred in the test group, the difference between the groups is not statistically significant in respect to mortality ($p \leq 0.05$).

Table 1:- The most frequent clinical presentations of the enrolled neonates (N=80).

CLINICAL PROFILE	CONTROL N= 40 MEAN (%)	TEST N=40 MEAN (%)	P VALUE
Reluctant To Feed	35(87.5%)	35(87.5%)	
Lethargy	38(95%)	35(87.5%)	
Temperature Instability	29(72.5%)	28(70%)	
Recurrent Apnea	28(70%)	29(72.5%)	
Abdominal distension	01(2.5%)	01(2.5%)	≥ 0.05
Bleeding tendencies	01(2.5%)	02(5%)	
Jaundice	16(40%)	18(45%)	
Dyspnea	35(87.5%)	33(82.5%)	
Vomiting	01(2.5%)	01(2.5%)	
Convulsions	01(2.5%)	01(2.5%)	
Fever	29(72.5%)	29(72.5%)	
Splenomegaly	00	00	
Diarrhea	02(5%)	01(2.5%)	

Table 2:- Type of organisms found in positive blood cultures of the enrolled neonates (N=73).

ORGANISM	CONTROL	TEST	P VALUE
CITROBACTER SPS	01	01	≥0.05
KLEBSIELLA PNEUMONIA	18	19	
STAPHYCOCCUS AUREUS	10	11	
STREPTOCOCCUS AUREUS	06	06	
COUGULASE NEGATIVE	01	00	

Table 3:- Immunoglobulin levels in neonates (test) before and after treatment with IVIG (N=40).

IMMUNOGLO BULIN LEVEL	NORMAL RANGE (mg/dL)	BEFORE STUDY (MEAN±SD)	AFTER STUDY (MEAN±SD)	P VALUE
Ig G	600-1465	626.18±85.20	865.63±93.03	≤0.05
Ig M	06-34.7	8.20±1.62	10.05±1.92	≤0.05
Ig A	1.3-42	3.63±0.90	8.30±1.40	≤0.05

Discussion:-

In our study both the study and control-groups were practically identical on sex, birth weight, gestational age, mean age, and clinical profile ($p \leq 0.05$). Systemic infection in the newborns is one of the common reasons for neonatal mortality. Information from National Neonatal Perinatal Database 2000 proposes that Klebsiella pneumoniae and Staphylococcus aureus are the commonest reasons for neonatal sepsis in India. Two structures of clinical introductions have been distinguished. Early onset sepsis, probably related to perinatal risk factors, usually presents with respiratory distress and pneumonia within 72 hours of age. Late onset sepsis, related to hospital acquired infections, usually presents with septicaemia and pneumonia after 72 hours of age.⁹ Clinical features of sepsis are nonspecific in neonates and a high index of suspicion is required for the timely diagnosis of sepsis. Although blood culture is the gold standard for the diagnosis of sepsis, reports are available after 48-72 hours. (12) A practical septic screen for the diagnosis of sepsis has been described and some suggestions for antibiotic use have been included in the protocol.¹⁰ In the present study, Klebsiella was observed to be the most regular organism bringing on sepsis in study (51.35%) and control (50%), which was trailed by STAPHYLOCOCCUS 27.77% and 29.72% in study and control groups respectively. The hospital stay of the test group (6.57 ± 2.10) is observed to be less than the control group (12.05 ± 5.43). It is found in our study that there are more cases of early onset sepsis when compared to late onset sepsis (Out of the total 80 patients, 48 were having EOS and 32 were having LOS). The babies who are born through LSCS have a slightly increased chance of acquiring sepsis than who are born through normal vaginal delivery (Out of the total 80 patients, 51 are having the history of LSCS and 29 are having the history of NVD). The explanation behind getting such a low immunoglobulin level is because of the way that untimely babies have low serum immunoglobulin levels during childbirth and don't begin creating apparent measures of endogenous immunoglobulin until they are no less than 24 weeks old. Untimely newborn children of 32 weeks of growth or less are especially traded off, their IgG focuses being obligated to tumble to 200 mg/dl as right on time as a month and a half after birth. An infant conceived at term at a comparative postnatal age has a serum iGg convergence of around 600 mg/dl.¹¹

Conclusion:-

From the findings of our study it can be concluded that the administration of IVIG is a useful and effective adjunctive therapy when compared with that of antibiotic therapy alone for the antibacterial defences in newborn infants with septicaemia and also reduces the length of hospital stay and is found to decrease the mortality rate of neonates with sepsis.

Acknowledgement:-

The authors would like to thank the hospital medical staff for their helping in retrieving the medical records. There was no funding received for this research. The authors report no conflict of interest in this work.

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