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# A STUDY TO ASSESS THE IMPORTANCE OF INTRAVENOUS IMMUNOGLOBULIN (IVIG) AS AN ADJUVANT IN THE TREATMENT OF NEONATAL SEPSIS IN PRETERM BABIES

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**Abstract:**
***Introduction:*** *Newborn children conceived before 32 weeks of incubation are genuinely immune deficient with cord blood centralization of IgG being not as much as half contrasted with those found in infants conceived at full term. Furthermore, exceptionally preterm newborn children have lessened supplement components, polymorphonuclear chemotaxis and are obligated to debilitate their capacity pools.*
***Goals and Goals:*** *An attempt was made to conduct this planned study with accompanying goals to focus on administering IVIG in addition to antibiotics to improve the therapeutic consequences of sepsis in premature infants.*
***Materials and Methods:*** *Sixty preterm infants with sepsis were randomly assigned to study and control groups in the Neonatal Intensive Care Unit of Fauji Foundation Hospital, Rawalpindi for one-year duration from May 2019 to April 2020. The study group was given IVIG in addition to standard treatment.*
***Results:*** *A total of 60 patients were enrolled, 30 in the study and 30 in the control group. There were no differences between the sexes (male 50%, females 50%) of the included newborns, which is also visible in the study (men 47.7%, women 52.3%) and the control group (males 52.3%, females 47.7 %).*
***Conclusion:*** *The low level of immunity in premature babies causes increased morbidity and mortality in severe infections. Using IVIG along with antibiotics and other supportive therapies may improve outcome.*
**Key words:** *IVIG, neonatal sepsis, premature babies.*

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## INTRODUCTION:

Neonatal sepsis is characterized by disease in newborns who are less than 28 days old, are clinically ill and have positive blood cultures for culture. the incidence of neonatal sepsis varies from 2.2 / 1000 live births in developed countries to 10-50 / 1000 live births in developing countries; however, reporting is most common in both countries1-2. The incidence of premature babies rises to 4/1000 premature births. Notwithstanding the steady and significant advances in hygiene, the demonstration of more recent effective antimicrobials, and supported strategies in early analysis and treatment, neonatal sepsis remains one of the most important causes of mortality in this age group. The high mortality and morbidity despite improved anti-infective agents and innovative advances in life-support therapies have prompted the search for different treatments3-4. Newborns are viewed as immunocompromised in terms of their moderately immature defense mechanism. In particular, they show a quantitative and additionally subjective inadequacy in their humoral insensitivity. A preterm newborn is even more at risk as the exchange of antibodies across the placenta begins after 32 weeks of growth and endogenous connection does not begin until approximately 24 weeks after birth. Newborns conceived before the 32nd week of incubation are truly immunodeficient, and the centralization of IgG in the umbilical cord blood is not half contrasted with that of termed infants5-6. Moreover, extremely premature babies have a reduced amount of supplement ingredients, polymorphonuclear chemotaxis and are bound to weaken their resources. Hypothetical arguments regarding the use of intravenous immunoglobulin (IVIG) in an infant are exceptionally large7-8. Unlike common intramuscular serum globulins, IVIG can be administered to patients in large amounts, paying little attention to body size or muscle mass, with a low frequency of antagonist response, thus producing an immediate abnormal state of a specific immune response that may have a good therapeutic effect. All things considered, IVIG administration has been proposed to prevent and treat bacterial sepsis in newborns. Several reviews have shown a lower risk of death in neonates with sepsis who have received anti-infective agents in addition to IVIG, compared with young babies who have been given only antibacterial agents9-10. Likewise, newborns who are septic and unresponsive to standard antimicrobial therapy and continuous measures may benefit from IVIG therapy. IVIG regulated following clinical effects may increase survival in neonates with sepsis. Taking all of the above into account, administration of IVIG has been proposed to prevent and treat bacterial sepsis in neonates. The purpose of this review is to find out whether administration of IVIG in conjunction with antimicrobial drugs improves sepsis outcomes in premature babies in our environment.

## MATERIALS AND METHODS:

This prospective, randomized, controlled study was conducted among sixty preterm infants with sepsis and randomly assigned to study and control groups in the Neonatal Intensive Care Unit of Fauji Foundation Hospital, Rawalpindi for one-year duration from May 2019 to April 2020.

**Study population:**

Preterm infants less than 33 weeks of age with suspected sepsis were eligible for inclusion. After admission to the hospital, the gestational age was determined on the basis of maternal dates (time from the main day of the last menstruation) and confirmed using the Ballard scale. A point-by-point history was collected, a thorough physical examination was performed and recorded in a standardized questionnaire. Sepsis has been associated by the presence of clinical signs that are reliable with possible true bacterial disease, including lethargy, refusal to eat, stomach bloating, heaving, snorting, grimacing, breathing problems, hypothermia, fever, or Sclerema neonatorum with or without risk confirmation on for example, maternal asphyxia, inflammation of the membranes of the mother's membranes (maternal fever or potentially rotten vaginal discharge) and delayed bursting of the layers. Meningitis has been associated with a history of seizures, screeching crying, and protruding / taut anterior fontanelles along with various sepsis components. Patients with respiratory distress (RDS), internal net abnormalities, and prior antitoxin treatment were avoided. The infants were sorted according to the associated sepsis risk factors: sex, birth weight, gestational age, origin, and mode of transmission. After admission to the study, the patients underwent the following diagnostic procedures: blood count, blood culture, and C-reactive protein (CRP) determination. In the case of suspected meningitis, CSF culture was performed.

Neonatal sepsis was diagnosed when the clinical suspicion was confirmed by a positive blood and / or cerebrospinal fluid culture or by a clinical and biochemical test, e.g. CRP (> 10 mg / dl), striated form (IT ratio> 0.2) and leukocytosis or leukopenia.

**Procedures:**

After the likely responses and benefits of IVIG were explained, explained, and consented to caregivers,

neonatal babies were arbitrarily assigned individually to study and control groups. The test group was treated with IVIG in addition to the standard neonatal sepsis treatment protocol, while the control group was given the standard treatment convention without IVIG. IVIG was administered as a moderate intravenous mixture at a dose of 500 mg / kg once daily for 3 consecutive days. The recommended immunoglobulin concentration is 50 mg / ml of solution for injection (infusion) provided in a 1 g (20 ml) single use ampoule. Newborns in both groups received similar general care. We collected a primary blood test for immunoglobulin levels before IVIG administration and after 2 days after IVIG administration. Immunoglobulin levels were determined by ELISA technique. Two milliliters of blood were drawn from the peripheral vein with a disposable syringe, and the isolated serum was left to stand at -200 ° C until immunoglobulin levels were tested using an immunodiffusion system in accordance with the ELISA package instructions. Treatment outcome was recorded on the basis of the total number of days the infant needed to remain in the facility and the death rate for both groups. The "hospital stay" was characterized as the expected time it takes to heal the problem or its related complications and then discharge. "Mortality" includes those who died in hospital from sepsis, rash, or related complications. Patients were discharged from the hospital when there was no antibacterial agent present, the baseline capabilities were stable, and oral feeding was established. The ward arrangement was "possible early discharge" to prevent nosocomial infection and accommodate new patients in the line. The discharge was decided by the advisers of individual units; for study reasons other than administration of intravenous immunoglobulin, no decision was made by the patient.

**Statistical analysis:**

The data was statistically analyzed according to a standard procedure. Statistical analysis was performed using Microsoft Word, Microsoft Excel and Epi Info 7.

## RESULTS:

A total of 60 patients were enrolled in the study, 30 in the study and 30 in the control group. There were no differences between the sexes (men 50%, women 50%) of the included newborns, which is also visible in the study (men 47.7%, women 52.3%) and the control group (men 52.3%, women 47.7 %). The mean birth weight of the study group was 1450 g with a standard deviation of 290 g, and the newborns from the control group was 1560 g with a standard deviation of 300 g.

**Table 1 Baseline characteristics of enrolled neonates (N=60)**

| Variables | Baseline characteristics Mean ± SD (%) | Study Group (N=30) Mean ± SD (%) | Control Group (N=30) Mean ± SD (%) | p value |
|---|---|---|---|---|
| Birth weight | (in Kg) | 1.40 ± 0.27 | 1.51 ± 0.28 | p>0.05 |
| Gestational age | (in weeks) | 31.83 ±1.86 | 31.82 ± 1.70 | p>0.05 |
| Age | (in days) | 12.88 ± 4.13 | 13.32 ± 3.86 | p>0.05 |
| Sex | Male | 14 (47.7) | 16 (52.3) | p>0.05 |
| | Female | 16 (52.3) | 14 (47.7) | p>0.05 |
| Blood culture | Positive | 22 (73.3) | 21 (70.0) | p>0.05 |
| | Negative | 08 (26.7) | 09 (30.0) | p>0.05 |
| CRP Level | High | 22 (73.3) | 22 (73.3) | p>0.05 |
| | Normal | 08 (47.7) | 08 (47.7) | p>0.05 |

The mean gestational age of children was 31.83 ± 1.86 weeks in the study group and 31.82 ± 1.70 weeks. in the control group. The mean age on admission was 12.88 ± 4.13 days and 13.32 ± 3.86 days in the study and control groups, respectively. The minimum and maximum age of the newborns was 3 days and 19 days. There was no significant difference between the groups in terms of birth weight, gestational age, admission age, or socio-demographic characteristics (p> 0.05) (Table 1). The most common clinical symptoms were reluctance to eat (83.3%), lethargy (90%), hypothermia (50%), apnea (73.3%), flatulence (66.6%), bleeding tendency (50%), jaundice (43.3%)) and respiratory failure (16.7%).

**Table 2 Clinical Profile of neonates with neonatal sepsis (N=60)**

| Clinical Profile | Study Group (N=30) Mean (%) | Control Group (N=30) Mean (%) | p value |
|---|---|---|---|
| Reluctant to feed | 25 (83.3) | 27 (90.0) | p>0.05 |
| Lethargy | 27 (90.0) | 26 (86.7) | p>0.05 |
| Temperature instability | 15 (50.0) | 18 (60.0) | p>0.05 |
| Recurrent Apnea | 22 (73.3) | 18 (60.0) | p>0.05 |
| Abdominal distension | 20 (66.6) | 16 (53.3) | p>0.05 |
| Bleeding tendency | 15 (50.0) | 16 (53.3) | p>0.05 |
| Jaundice | 13 (43.3) | 09 (30.0) | p>0.05 |
| Dyspnea | 10 (16.7) | 05 (8.7) | p>0.05 |
| Vomiting | 04 (13.3) | 03 (10.0) | p>0.05 |
| Convulsions | 04 (13.3) | 03 (10.0) | p>0.05 |
| Fever | 05 (16.7) | 02 (06.7) | p>0.05 |
| Splenomegaly | 04 (13.3) | 03 (10.0) | p>0.05 |
| Septic foci | 04 (13.3) | 01 (03.3) | p>0.05 |
| Diarrhea | 02 (06.6) | 01 (03.3) | p>0.05 |

The statistical test showed that both groups were identical in terms of the clinical picture (Table 2). A complete blood culture showed that approximately (73.3%) of the cases were positive and 26.7% negative in the test group. In the control group, cases were positive (70%) and negative (30%). High CRP was found in 70% of the examined and control group.

Of the 43 culture-positive neonates, 97.8% had Gram-negative bacilli, and only 1 (2.2%) had Gram-positive bacteria. The most common organism was Klebsiella pneumoniae (53.3%, 24/45), followed by Acinetobacter (24.5%, 11/45) and pseudomonas (15.5%, 7/45). The pattern of isolated organisms was similar in both groups (Tab. 3).

**Table 3 Organisms causing sepsis in culture positive neonates (N=45)**

| Baseline characteristics (%) | Study Group (N=23) (%) | Control Group (N=22) (%) |
|---|---|---|
| *Klebsiella* | 12 (52.17) | 13 (59.0) |
| *Pseudomonas* | 04 (17.4) | 03 (13.6) |
| *Acinetobacter* | 05 (21.8) | 06 (27.2) |
| *Salmonella* | 02 (8.6) | 01 (4.6) |
| *Staphylococci* | 0 (00.0) | 01 (4.6) |
| Total | 23 (100) | 22 (100) |

Most of the organisms were resistant to commonly used antibiotics. The third-generation cephalosporin, ciprofloxacin and imipenem were the most sensitive to all isolates. In more than half of the cases, netilmicin and gentamicin were also sensitive. IgM, IgG and IgA levels were only performed in the test group before and after IVIG treatment to see the changes in their levels in two steps. A t-test was performed and statistically significant changes were found in all three immunoglobulin levels after IVIG treatment ($p < 0.0001$) (Table 4).

**Table 4 Immunoglobulin level in patients (Study group) before and after treatment with IVIG**

| Immunoglobulin level | Normal range (mg/dl) | Before study (mg/dl) | After study (mg/dl) | t-test (p value) |
|---|---|---|---|---|
| Immunoglobulin G | 600-1465 | 621 ± 153.71 | 785 ± 118.53 | 18.35 (p<0.0001) |
| Immunoglobulin M | 6-34.7 | 7.74 ± 2.14 | 11.08 ± 2.84 | 13.52 (p<0.0001) |
| Immunoglobulin A | 1.3-42 | 4.34 ± 2.32 | 8.35 ± 4.65 | 14.48 (p<0.0001) |

A statistical t-test was performed to see the difference between the two groups in terms of hospital stay and the c2 test to see the difference in mortality between the groups. The mean stay of the study group in the hospital was 14.53 ± 3.88 days, with a minimum of 7 days and a maximum of 21 days. On the other hand, the mean duration of hospital stay in the control group was 18.30 ± 6.88 days, with a minimum of 3 days (1 patient being discharged after 3 days under a risk agreement) and a maximum of 35 days. The difference between the two groups was found to be statistically significant (t = 2.6, p <0.05). Of the 60 patients in both groups, 46 (76.7%) were discharged from the hospital after recovery. Mortality was lower in the study group, but the difference between the two groups was not statistically significant (c2 = 3.35, p = 0.06).

## DISCUSSION:

In our study, both the test and control groups were practically identical in terms of sex, birth weight, gestational age, mean age and clinical profile (p> 0.05). The clinical picture of our patients in Table 2 is reliable relative to the results of other comparative studies and is further described in standard pediatric manuals[11]. In developed countries, group B streptococci and coagulase negative staphylococci are the most commonly known etiological factors, respectively, anticipating the early and late onset of neonatal sepsis. Either way, in developing countries these organisms are rare and have a completely unique range of bacteria; Escherichia coli and Klebsiella are the best-known organisms that cause sepsis in newborns. This thought proved correct if the current study and other studies conducted in developing countries occurred. In the present study, it was observed that Klebsiella was the most regular sepsis-causing organism in the study (56.5%) and the control group (50%), followed by 21.8% and 27.2% separate Pseudomonas in the test and control groups. no development of group B Streptococcus was found, and only one case was Staphylococcus. In a study conducted in a similar ICU in 2013, almost three-quarters (73%) of organisms disconnected from blood in neonatal sepsis were gram-negative bacilli. Nevertheless, Escherichia coli was the most famous organism at the time, followed by Klebsiella pneumoniae (23%) and Pseudomonas (10%)[12]. Among gram-positive organisms. Staphylococcus aureus was found in 16.7% of isolates. Such a significant change in the isolation pattern from the same facility two years apart may be due to the way in which the etiology of neonatal sepsis may change over time within a given topographic area. For this reason, periodic reconnaissance is recommended for disease specialists and their infection susceptibility profiles. Characteristic reviews in Pakistan have also shown that gram-negative organisms are the transcendent cause of neonatal sepsis. In the blood of preterm, contrast-born and full-term infants, the level of IgG is lower during labor and the faster it falls to a lower fixation. The explanation for getting such a low immunoglobulin level is the way preterm babies have low serum immunoglobulin levels during labor and do not begin to form spurious endogenous immunoglobulin measures until they are at least 24 weeks old. Premature babies of 32 weeks of age or younger are specifically replaced, their IgG is required to drop to 200 mg / dL as soon as one and a half months after birth. An infant conceived at a comparable postpartum age has a serum IgG convergence of approximately 600 mg / dL[13]. Since IgM and IgA are impermeable to placental obstruction; their levels during childbirth are low compared to adult levels. The high amounts of IgM and IgA in this review may be due to subclinical intrauterine infection or due to disease of the newborns after birth. In a review by Fischer et al., Mean neonatal preterm IgG levels were 368 mg / dL at birth, fell to 104 mg / dL at 3 months of age, and then gradually increased. In their review, Weisman et al. Observed a remarkable increase (p <0.05) in serum IgG in patients treated with IVIG. Kinney et al. similarly, it was observed that the mean IgG levels achieved prior to each dose received were generally higher in IVIG-treated neonates than in the placebo treatment arrangements (p <0.05). In another review on "IVIG treatment of early sepsis in premature babies," Weisman et al. Showed that in patients with early-onset sepsis, the sum of serum IgG levels was generally increased following IVIG infusion in correlation with albumin. While in our test group it was 621 mg / dl. Perception of length of stay in a facility is similar to that of other large-scale studies

planned at various centers. Conway in his research revealed that infants in the treatment group had a shorter stay in the ICU (p = 0.001)[14]. Lassiter detailed that IVIG administration was associated with a reduction in hospitalization time. In another randomized review by Kinney et al., The mean in-home stay for patients receiving IVIG was 43.1 days (36.3-49.9), which is 46.5 days (39-54) for the placebo group. However, in another multicenter randomized review conducted in Pakistan, researchers found hardly any difference in the length of inpatient studies between the three groups: 18.3 ± 2.34 days on placebo treatment, 17 ± 2.08 days in the IVIG group, and 13.3 ± 2.91 days in the control group. Mortality was significantly lower in the IVIG group (13.3%) compared to the control group (33.3%). Although the difference in mortality between the two crops was not measurably large (c2 = 3.35, p = 0.06), the rather slope indicates that the mortality was significantly lower in the study group. Reviews directed to different hospitals at different times show mixed results if there is a reduction in mortality in newborns treated with IVIG with neonatal sepsis. Sidiropoulos was the principal investigator who reported the use of IVIG to treat barbaric neonates with bacterial sepsis. In his review, the death rate was 27% (4/15) in the control group and 10% (2/20) among IVIG beneficiaries (p = 0.016). IVIG treatment had all the characteristics of the best outcome in low birth weight septic neonates. Consolidation of the four reviews that examined the usefulness of IVIG showed that the event occurred in 9% (6/67) of IVIG beneficiaries, in contrast and 30% (20/67) of the controls. Weisman et al. in their review showed that there were 29.41% (5/17) deaths in control patients compared with 11.76% (2/14) deaths in IVIG-treated neonates[15]. In another study, the mortality rate was equivalent (17.5%) in both groups of preterm infants. In another multicenter study in Pakistan, it was additionally observed that the mortality was the same (28%) in the three groups: placebo, IVIG, and control. Haque et al. in their two studies concluded that the mortality from sepsis is substantially lower in the IVIG treated groups (p <0.001).

## CONCLUSION:

From the results of this study, it can be concluded that IVIG is a useful adjunct to antimicrobial defense in neonates with sepsis.

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