Role of Intravenous Immunoglobulin (IVIG) as an Adjuvant in the Treatment of Neonatal Sepsis in Preterm Babies

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Summary:

Neonates are considered immunocompromised in view of their relatively immature immune defense mechanisms. Intravenous immunoglobulin (IVIG), in combination with antibiotic therapy in sepsis, has been reported to decrease the mortality and morbidity in preterm neonates. Sixty preterm neonates with sepsis were randomly assigned into study and control groups. Study-group was given IVIG in addition to standard treatment. The outcome measures were immunoglobulin levels before and after IVIG therapy in study-group, duration of hospital stay and mortality rate between the groups. IgG level was 529.16 ± 147.73 mg/dl and 886.83 ± 120.73 mg/dl; IgM 7.74 ± 2.14 mg/dl and 11.08 ± 2.84 mg/dl, and IgA 5.34 ± 2.24 mg/dl and 9.28 ± 3.26 mg/dl before and after IVIG infusion. This difference was found statistically significant (p<0.0001). The mean duration of hospital stay of study and control group was 14.53 ± 3.88 days and 18.30 ± 6.88 days respectively. This difference was also statistically significant (p<0.05). The mortality rate was much lower in study group (13.3 %) compared to the control group (33.3%). Low levels of immunity in preterm neonates results in increased morbidity and mortality in severe infection. Use of IVIG along with the antibiotics and other supportive therapy can improve the outcome.

(J Bangladesh Coll Phys Surg 2006; 24 : 97-104)

Introduction:

Neonatal septicaemia is defined as a disease of the infants who are younger than one month of age, are clinically ill, and has positive blood cultures[1]. Incidence of neonatal sepsis varies from 2.2/1000 live births in developed countries to 10-50/1000 live births in developing countries; though under reporting is common in both[2]. Incidence in preterm infants rises to 4/1000 live premature births[1,2]. Despite considerable progress in hygiene, introduction of newer effective antimicrobial agents and advanced techniques in early diagnosis and treatment, neonatal septicaemia still remains one of the most important causes of mortality in this age group[3,4]. The high mortality and morbidity rates despite improved antibiotics and technological advancements in life support therapy have led to the search for other modalities of treatment.

Neonates are considered immunocompromised in view of their relatively immature immune defense mechanisms. Specifically, they have quantitative as well as qualitative deficiency in their humoral immunity. The preterm neonate is at further risk, as transplacental transfer of antibodies starts after 32 weeks of gestation and endogenous synthesis does not begin until about 24 weeks after birth.[5] Infants born before 32 weeks' gestation are seriously immunodeficient with cord blood concentration of IgG being less than half those found in babies born at full term[6]. In addition, very preterm infants have reduced complement factors, opsonic activity, polymorphonuclear chemotaxis and are liable to exhaust their storage pools[7].

Theoretical arguments for the use of intravenous immunoglobulin (IVIG) therapy in the newborn are very strong. In contrast to conventional intramuscular serum globulins, IVIG can be given in large quantities to patients, regardless of body size or muscle mass, with a low incidence of adverse reaction, thereby providing immediate high level of specific antibody that may be of therapeutic benefit[8]. Considering all the above, the administration of IVIG has been proposed for the prevention and treatment of bacterial sepsis in neonates.

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Several studies have shown a lower risk of death in septic neonates given antibiotics plus IVIG, compared to children given antibiotics only[4-6,9]. Also neonates who are septic and not responding to standard antibiotic treatment and supportive measures might be benefited by IVIG therapy[10]. IVIG administered after the onset of clinical symptoms may improve the survival of septic human neonates[11]. Considering all the above, administration of IVIG has been proposed for the prevention and treatment of bacterial sepsis in neonates.

The present study is designed to find out whether administration of IVIG in conjunction with antibiotics improves the outcome of sepsis in preterm neonates in our setting.

Materials and methods:

Study site: This prospective, randomized, controlled, non-blind intervention trial was conducted in the special care nursery of Dhaka Shishu Hospital, Dhaka, Bangladesh from June 2000 to November 2001. The hospital is the largest tertiary care pediatric center in Bangladesh with 24 beds in the nursery and serves the paediatric patients from all sections of the population. There is no attached obstetric unit, thus patients were received from different parts of Dhaka city as well as from remote areas of the country.

Study population: Preterm neonates < 33 weeks' gestation with suspected septicaemia were eligible for enrollment. After admission into the hospital gestational age was determined from maternal dates (time from the first day of the last menstrual period) and confirmed by Ballard scoring system[12]. Detailed history was taken and thorough physical examination was performed and recorded on standard forms. Septicaemia was suspected based on the presence of clinical signs consistent with possible serious bacterial infection including lethargy, refusal of feeds, abdominal distension, vomiting, groaning, grunting, facial grimace, respiratory distress, hypothermia, fever or sclerema with or without supporting evidence of risk factors such as birth asphyxia, maternal chorioamnionitis (maternal fever and/ or foul smelling vaginal discharge) and prolonged rupture of membranes. Meningitis was suspected from a history of convulsion, high-pitched cry and full, tense anterior fontanel along with other features of septicaemia. The patients with respiratory distress syndrome (RDS), gross congenital anomalies and any

previous antibiotic therapy were excluded. The babies were categorized according to the following risk factors for septicaemia: sex, birth weight, gestational age, birthplace and mode of delivery.

Laboratory investigations: After enrollment, the patients underwent the following diagnostic procedures: complete blood count, blood culture and C - reactive protein (CRP) estimation. CSF culture was done in cases of suspected meningitis.

Diagnosis: A diagnosis of neonatal septicaemia was made when the clinical suspicion was confirmed by a positive blood and/or CSF culture or by clinical and biochemical examination e.g. CRP (>10mg/dL), band form (IT ratio >0.2) and leucocytosis or leucopenia.

Procedures: After explaining the probable side effects and benefits of IVIG to the parents and taking informed consent from them, the consecutive neonates were randomly assigned into study and control groups respectively. The study group was treated with IVIG in addition to standard treatment protocol for neonatal sepsis, whereas control group was given the standard treatment protocol without IVIG. IVIG was given as slow intravenous infusion at a dose of 500 mg/kg once daily for 3 consecutive days. Concentration of prescribed immunoglobulin was 50 mg/ml solution for infusion supplied in 1 g (20 ml) single use bottle. Infants in both groups otherwise received the same general care. We collected the first blood sample for immunoglobulin level before IVIG administration and for post treatment level after 2 days of completion of IVIG administration. The immunoglobulin levels were determined by ELISA method. Two millilitres of blood was drawn from a peripheral vein by disposable syringe and the separated serum was stored at –20ºC till testing the immunoglobulin levels by using radial immunodiffusion technique as per instructions given in the ELISA kit.

Outcome: Outcome of treatment was recorded by total number of days the child had to stay in the hospital and mortality rate of the two groups. 'Hospital stay' was defined as the time needed to cure from the problem or its associated complication and discharge and 'mortality' as those who died in hospital either due to sepsis, prematurity or its complications. Patients were discharged when no antibiotic was necessary, vital functions were stable and oral feeding was established.

The policy of the ward was 'possible early release' to prevent a nosocomial infection and to accommodate new patients in queue. The decision of discharge was taken by the respective unit consultants; for study purpose, other than giving IV immunoglobulin no patient care decision was taken.

Statistical analysis: The data were subjected to statistical analysis according to standard procedure. SPSS version 10.1 for Windows (SPSS Inc, Chicago, IL, USA) software was used for data recording and analysis. Results of the findings were verified by doing standard test for significance like unpaired student "t" test and chi-square (χ^2) tests, as appropriate. A p-value of <0.05 was considered as statistically significant.

Results:

Total 60 patients were enrolled, 30 in study and 30 in control group. There were no gender differences (male 51.7%, female 48.3%) of neonates enrolled, which is also evident in the study (males 50%, females 50%) and control group (males 53.3%, females 46.7%). The mean birth weight of study group was 1450 gm with a standard deviation of 290 gm and control group neonates were 1560 gm with a standard deviation of 300 gm. The mean

gestational age of the babies was 30.93 ± 1.96 weeks in study group and 30.87 ± 1.80 weeks in control group. The mean age on admission were 9.80 ± 4.13 days and 10.30 ± 4.06 days in the study and control groups respectively. The minimum and maximum ages of the neonates were 3 days and 19 days. There was no significant difference between the groups in respect of birth weight, gestational age, admission age or socio-demographic characteristics (p>.05) (Table 1).

The most frequent clinical presentations were reluctant to feed (90%), lethargy (83.3%), hypothermia (65%), apnea (60%), abdominal distension (54.6%), bleeding tendency (50%), jaundice (28.3%) and respiratory distress (18.3%). Statistical test showed that the two groups were identical in respect of clinical presentation (Table 2).

Complete blood count revealed that 53.3% of study and 72.2% of control group had leucocytosis, thrombocytopenia was present in 63.3% and 66.6% of study and control groups respectively. CRP was found high among 70% of both study and control groups. Blood culture was found to be positive in three-fourths of the cases (study group 76.7% and control group 73.3%) (Table 1).

Table-I

Baseline characteristics	Study group (%)	Control group (%)	p-value
Number	30	30	
Birth weight (in kg) ± SD	1.45 ± .29	1.56 ± .30	>.05
Mean Gestational age (in weeks) ± SD	30.93 ± 1.96	30.87 ± 1.80	>.05
Mean Age (in days) ± SD	9.80 ± 4.13	10.30 ± 4.06	>.05
Sex			>.05
Male	15 (50.0)	16 (52.3)	
Female	15 (50.0)	14 (47.7)	
Blood Culture			>.05
Positive	23 (76.7)	22 (73.3)	
Negative	07 (22.3)	08 (26.7)	
CRP level			>.05
High	21 (70.0)	21 (70.0)	
Normal	09 (30.0)	09 (30.0)	

Baseline characteristics of enrolled neonates (n=60)

Of the 45 culture positive patients, 97.8%, 44/45 had gram-negative bacilli, only 1 (2.2%) had gram-positive. *Klebsiella pneumoniae* was the most common organism (53.3%, 24/45), followed by *pseudomonas* (24.5%, 11/45) and *Acinetobacter* (15.5%, 7/45). The pattern of organisms isolated was similar in both groups (Table 3). Most of the organisms were resistant to commonly used antibiotics. Third generation cephalosporins, ciprofloxacin and imipenem were mostly sensitive to all the isolates. In more than half of the cases netilmicin and gentamicin was also found sensitive[13].

IgM, IgG and IgA level were done only in study group before and after treatment with IVIG to see the changes in their levels at two stages. Student t-test was done and statistically significant changes were found in all three immunoglobulin levels after treatment with IVIG (p<.0001) (Table 4).

Statistical t-test was done to see the difference between the two groups in respect of hospital stay and c^2 - test to see the difference in mortality between the groups. The mean hospital stay of study group was 14.53 days $\pm$ 3.88 days with minimum of 7 days and maximum 21 days. On the other hand the mean duration of hospital stay of the control group was 18.30 days $\pm$ 6.88 days with minimum of 3 days (1 patient discharged after 3 days on risk bond) and maximum 35 days (Figure 1). This difference between the two groups was found to be statistically significant (t=2.6, p<.05). Out of total 60 patients in both groups, 46 (76.7%) were released from the hospital when they were cured. Mortality was 13.3 % in the group treated with IVIG in comparison to 33.3% in the control group (Figure 2). The mortality rate was lower in study group but the difference between the two groups was not statistically significant (c^2= 3.35, p=.06).

Table-II

Clinical Profile of the neonates with neonatal sepsis (n=60)

Clinical Profile	Study group (%)	Control Group (%)	p-value
Reluctant to feed	28 (93.3)	26 (86.7)	>.05
Lethargy	26 (86.7)	24 (80.0)	>.05
Temperature instability	23 (76.7)	16 (53.3)	>.05
Recurrent apnea	16 (53.3)	20 (66.6)	>.05
Abdominal distension	18 (60.0)	16 (53.3)	>.05
Bleeding tendency	14 ((46.7)	16 (53.3)	>.05
Jaundice	11 (36.7)	06 (20.0)	>.05
Dyspnoea	05 (16.7)	10 (16.7)	>.05
Vomiting	03 (10.0)	04 (13.3)	>.05
Convulsion	03 (10.0)	04 (13.3)	>.05
Fever	02 (6.7)	05 (16.7)	>.05
Splenomegaly	03 (10.0)	04 (13.3)	>.05
Septic foci	04 (13.3)	01 (1.7)	>.05
Diarrhoea	01 (1.7)	0	>.05

Table-III

Organisms causing sepsis in culture positive patients (n=45)

Organisms	Study group (%)	Control group (%)
Klebsiella	13 (56.5)	11 (50.0)
Pseudomonas	05 (21.8)	06 (27.2)
Acinetobacter	04 (17.4)	03 (13.6)
Salmonella	01 (4.3)	01 (4.6)
Staphylococci	0	01 (4.6)
Total	23 (100)	22 (100)

Table-IV

Immunoglobulin level in patients (Study group) before & after treatment with IVIG

Immunoglobulin Level	Mean (mg/dl) (± SD) Before Study	Mean (mg/dl) (± SD) After Study	"t"-test	P-value
Immunoglobulin G <.0001 (Normal 600- 1465 mg/dl)	529.16 ± 147.73	886.83 ± 120.73	20.45	
Immunoglobulin M <.0001 (Normal 6- 34.7 mg/ dl)	7.74 ± 2.14	11.08 ± 2.84	12.61	
Immunoglobulin A <.0001 (Normal 1.3 – 42 mg/dl)	5.34 ± 2.24	9.28 ± 3.26	12.38	
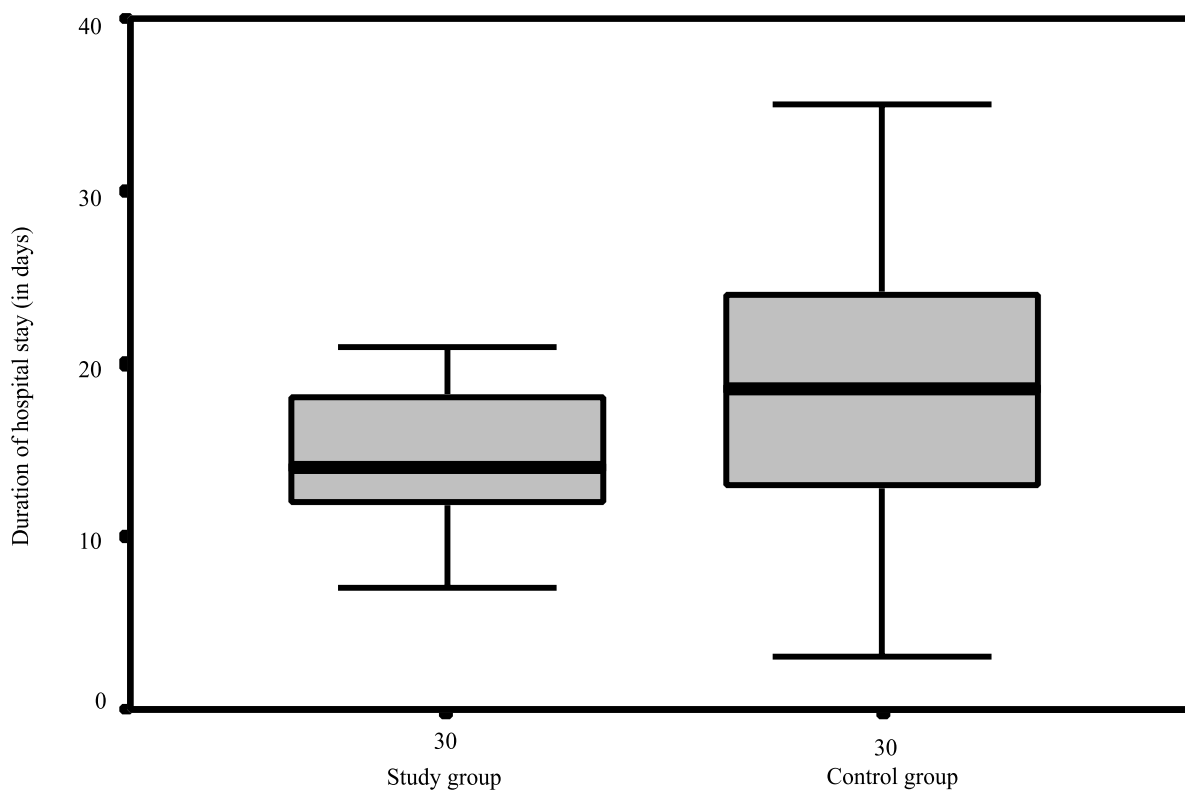
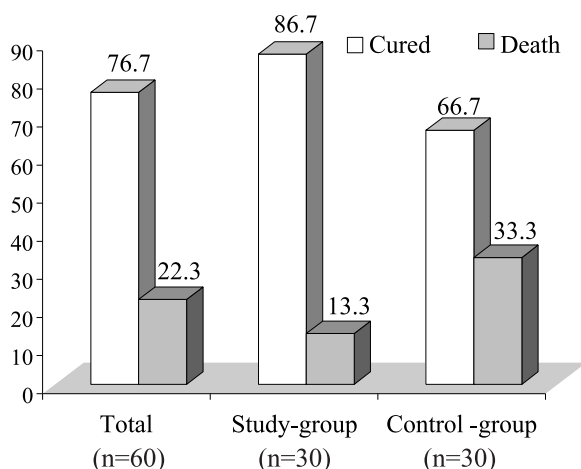**Fig.-1:** *Duration of hospital stay compared (n=60)*

Fig 2: *Outcome of treatment with and without IVIG (n=60)*

Discussion:

In this study both the study- and control- groups were comparable for sex, birth weight, gestational age, mean age and clinical profile (p>.05). The clinical presentation of our patients (Table 2) is consistent to those found in other similar studies as well as narrated in the standard paediatric text books[14-17].

In developed countries, Group B Streptococcus and coagulase negative Staphylococci are the most common etiological agents for early and late onset neonatal sepsis respectively. However, in developing nations these organisms are rare with an entirely different bacterial spectrum; *E. coli* and *Klebsiella* are the most common organisms causing neonatal septicemia[1]. This notion is proved to be true in case of the present study and other studies done in the developing countries[18,19]. In the present study, *Klebsiella* was found to be most common organism causing sepsis in study (56.5%) and control group (50%), which was followed by *Pseudomonas* 21.8% and 27.2% in study and control groups respectively. There was no growth of Group-B Streptococcus, and Staphylococcus was found only in one case. In one study conducted in the same nursery in 1998, nearly three fourths (73%) of the isolated organisms from blood in neonatal septicemia were Gram-negative bacilli. But *E. coli* was then the most common organism followed by *Kl. pneumoniae* (23%) and *Pseudomonas* spp. (10%). Among the Gram-positive organisms *Staphylococcus aureus* was found in 16.7% of the isolates[20]. Such remarkable change in isolation pattern from same hospital two years apart may be due

to the fact that etiology of neonatal septicaemia may change within a geographical location with time[21-24]. Because of this, periodic surveillance for agents of infection and their antibiotic sensitivity profiles is recommended. Different studies done in India also showed Gram-negative organisms were predominant cause of neonatal sepsis[14,18].

In the blood of preterm neonates, compared with fullterm, the IgG concentration is lower at birth and declines more rapidly to a lower concentration. The reason for getting such a low immunoglobulin level is due to the fact that premature babies have low serum immunoglobulin concentrations at birth and do not start producing appreciable amounts of endogenous immunoglobulin until they are at least 24 weeks old. Premature infants of 32 weeks' gestation or less are particularly compromised, their IgG concentrations being liable to fall to 200 mg/dl as early as six weeks after birth. A baby born at term at a similar postnatal age has a serum IgG concentration of about 600 mg/dl[25]. Since IgM and IgA are impermeable to placental barrier; their levels at birth are very low as compared to adult levels. High levels of IgM and IgA in the present study could be due to sub-clinical intrauterine infection or due to neonatal infection after birth[26].

In a study by Fischer GW the mean IgG concentration in premature neonates was 368 mg/dl at birth, declined to 104 mg/dl at 3 months of age and then slowly increased[10]. In their study, Weisman LE et al observed significant increase (p<0.05) of serum IgG in IVIG treated patients[27]. Kinney et al also observed that mean IgG levels obtained before each subsequent dose were significantly higher in IVIG treated neonates than in the placebo preparations (p<.05) [28]. In another study on "IVIG therapy for early onset sepsis in premature infants", Weisman LE et al observed that in patients with early-onset sepsis, total serum levels of IgG were significantly increased after infusion with IVIG in comparison with albumin[29].

The observation regarding the duration of hospital stay is similar to some other large prospective studies conducted at different centers. Conway SP in his study observed that the babies in treatment group had lesser stay in ICU (p=0.001) [25]. Lassiter HA reported that administration of IVIG was associated with a diminished length of hospitalization[11]. In another randomized,

double blind study conducted by Kinney et al the mean duration of hospital stay for patients receiving IVIG was 43.1days (36.3 – 49.9), which was 46.5 days (39 – 54) for placebo group[28]. Yet in another multicentre randomized study in Hyderabad, India, the researchers found very little difference in duration of hospital study among the three groups: 18.3 ± 2.34 days in placebo, 17 ± 2.08 days in IVIG group and 13.3 ± 2.91 days among the control group[9].

The mortality rate was much lower in the group treated with IVIG (13.3 %) in comparison to the control group (33.3%). Though the difference in mortality between the two groups was not statistically significant ($c^2=3.35$, p=.06), but the tendency shows that the mortality rate was much lower in the study-group. The studies conducted at different centers at different periods shows a mixed result in case of reduction of mortality rate in IVIG treated neonates suffering from neonatal sepsis. Sidiroplus in 1981, was the first investigator to report the use of IVIG to treat established bacterial sepsis in human neonates[30]. In his study the incidence of death was 27% (4/15) in controls and 10% (2/20) in the IVIG recipients (p=.016). IVIG therapy appeared to be most effective when administered to septic neonates of low birth weight. Combining the four studies designed to assess the therapeutic efficacy of IVIG revealed that death occurred in 9% (6/67) of IVIG recipients, compared with 30% (20/67) of control[10]. Weisman LE et al in their study observed that there was 29.41% deaths (5/17) in control patients against 11.76% deaths (2/14) in IVIG treated premature neonates[29]. The mortality rate was equal (17.5%) in both groups of premature neonates in another study[31]. In another multicentre study in Hyderabad, India, the mortality was also found to be same (28%) in three groups – placebo, IVIG and control[9]. Haque KN et al in their two studies concluded that the mortality from sepsis is significantly lower in the IVIG treated group (p<0.001) [32,33].

From the findings of the present study it can be concluded that the IVIG will likely serve as a useful adjunct for the antibacterial defenses in newborn infants with septicaemia. However, the safety and long-term consequences of administering IVIG to newborn premature infants are yet to be defined.

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