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A Study to Evaluate the Role of Intravenous Immunoglobulin (IVIG) as an Adjuvant in the Management 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.* ***Aims and Objectives:*** *This planned study has been attempted with the accompanying targets, to concentrate on the administration of IVIG in addition with antibiotics to improves the therapeutic consequence of sepsis in preterm neonates.* ***Materials and Methods:*** *Sixty preterm neonates with sepsis were randomly assigned into study and control groups at a tertiary level neonatal intensive care unit, Princess Esra Hospital and Owaisi Hospital & Research Centre, Deccan College of Medical Sciences, Hyderabad, Telangana, India. Study-group was given IVIG in addition to standard treatment.* ***Results:*** *Total 60 patients were enrolled, 30 in study and 30 in control group. There were no gender differences (male 50%, female 50%) of neonates enrolled, which is also evident in the study (males 47.7%, females 52.3%) and control group (males 52.3%, females 47.7%).* ***Conclusion:*** *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.*

Keywords: IVIG, neonatal sepsis, preterm babies

INTRODUCTION

Neonatal septicaemia is characterized as a disease of the newborn children who are younger than 28 days of age, are clinically sick, and has positive blood cultures of septicaemia [1]. prevalence of neonatal sepsis changes from 2.2/1000 live births in developed nations to 10-50/1000 live births in developing countries; however, under reporting is most common in both countries. Frequency in preterm newborn children ascends to 4/1000 live untimely births [1,2]. Not with standing extensive advance in hygiene, presentation of more up to date successful antimicrobials and propelled strategies in early analysis and treatment, neonatal septicaemia still stays a standout amongst the most imperative reasons for mortality in this age group [3,4]. The high mortality and morbidity rates in spite of enhanced anti-infection agents and innovative advancement in life bolster treatment have prompted to the scan for different modalities of treatment. Neonates are viewed as immune compromised in perspective of their moderately immature defence mechanism. In particular, they have quantitative and additionally subjective inadequacy in their humoral insusceptibility. The preterm neonate is at further hazard, as transplacental exchange of antibodies begins following 32 weeks of growth and endogenous combination does not start until around 24 weeks after birth [5]. Newborn children conceived before 32 weeks of incubation are genuinely immunodeficient with cord blood centralization of IgG being not as much as half contrasted with those found in infants conceived at full term [6]. Furthermore, exceptionally preterm newborn children have lessened supplement components, polymorphonuclear chemotaxis and are obligated to debilitate their capacity pools [7]. Hypothetical contentions for the utilization of intravenous immunoglobulin (IVIG) treatment in the infant are exceptionally outstanding. As opposed to ordinary intramuscular serum globulins, IVIG can be given in extensive amounts to patients, paying little mind to body size or bulk muscle mass, with a low frequency of antagonistic response, in this manner giving prompt abnormal state of particular immune response that might be of good therapeutic outcome [8].

Considering all over, the administration of IVIG has been proposed for the counteractive action and treatment of bacterial sepsis in neonates.

A few reviews have demonstrated a lower risk of death in septic neonates given anti-infection agents in addition to IVIG, contrasted with youngsters given anti-microbial only [4-6,9]. Likewise, neonates who are septic and not reacting to standard anti-microbial treatment and steady measures may be profited by IVIG therapy [10]. IVIG regulated after the onset of clinical effects may enhance the survival of septic neonates [11]. Considering all the above, administering of IVIG has been proposed for the avoidance and treatment of bacterial sepsis in neonates. The present review is intended to see if administering of IVIG in conjunction with anti-microbial enhances the result of sepsis in preterm neonates in our setting.

Aims and Objectives

This planned study has been attempted with the accompanying targets, to concentrate on the administration of IVIG in addition with antibiotics to improves the therapeutic consequence of sepsis in preterm neonates.

MATERIALS AND METHODS

This prospective, randomized, controlled study was conducted in a tertiary level neonatal intensive care unit of Princess Esra Hospital and Owaisi Hospital and Research Centre, Deccan College of Medical Sciences, Hyderabad, Telangana, India.

Study population

Preterm neonates <33 weeks of growth with suspected septicaemia were qualified for enlistment. After induction into the hospital facility gestational age was determined from maternal dates (time from the principal day of the last menstrual period) and affirmed by Ballard scoring framework [12]. Point by point history was taken and careful physical examination was performed and recorded on standard questionnaire. Septicaemia was associated in view of the presence of clinical signs reliable with possible genuine bacterial disease including lethargy, refusal of meals, stomach distension, heaving, snorting, facial scowl, respiratory trouble, hypothermia, fever or Sclerema neonatorum with or without supporting confirmation of risk components, for example, birth asphyxia, maternal chorioamnionitis (maternal fever or potentially putrid vaginal release) and delayed burst of layers. Meningitis was associated from a history of seizures, shrill cry, and protruding/tense foremost fontanel alongside different elements of septicaemia. The patients with respiratory distress disorder (RDS), net intrinsic abnormalities and any past anti-toxin treatment were avoided. The infants were sorted by the accompanying risk elements for septicaemia: sex, birth weight, gestational age, origin, and method of conveyance.

Laboratory investigations

After enrolment, 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 (>10 mg/dl), band form (IT ratio >0.2) and leucocytosis or leukopenia.

Procedures

After explaining and clarifying the plausible reactions and advantages of IVIG to the guardians and taking consent from them, the back to back neonates were arbitrarily assigned into study and control groups individually. The study group was treated with IVIG in addition to standard treatment protocol for neonatal sepsis, while control group was given the standard treatment convention without IVIG. IVIG was given as moderate intravenous mixture at a dosage of 500 mg/kg once every day for 3 consecutive days. Prescribed concentration of immunoglobulin was 50 mg/ml solution for imbuement (infusion) provided in 1 g (20 ml) single utilize ampule. Newborn children in both groups got a similar general care. We gathered the primary blood test for immunoglobulin level before IVIG administration and for post treatment level following 2 days of consummation of IVIG administration. The immunoglobulin levels were given by ELISA technique. Two millilitres of blood was drawn from a fringe vein by expendable syringe and the

isolated serum was put away at -200°C till testing the immunoglobulin levels by utilizing immunodiffusion system according to directions given in the ELISA pack.

Outcome

Result of treatment was recorded by aggregate number of days the infant needed to remain in the facility and death rate of the two groups. 'Hospital stay' was characterized as the time expected to cure from the issue or its related complications and then release. The "mortality" as the individuals who expired on in hospital's facility either because of sepsis, rashness, or its related complications. Patients were discharge when no anti-microbial was important, essential capacities were steady and oral feeding was established. The arrangement of the ward was 'possible early discharge' to prevent a nosocomial contamination and to suit new patients in line. The choice of discharge was taken by the separate unit advisors; for study reason, other than giving IV immunoglobulin no patient decision was taken.

Statistical analysis

The data were subjected to statistical analysis according to standard procedure. Using Microsoft word, Microsoft excels and Epi Info 7 Statistical analysis was done.

RESULTS

Total 60 patients were enrolled, 30 in study and 30 in control group. There were no gender differences (male 50%, female 50%) of neonates enrolled, which is also evident in the study (males 47.7%, females 52.3%) and control group (males 52.3%, females 47.7%). The mean birth weight of study group was 1450 g with a standard deviation of 290 g and control group neonates were 1560 g with a standard deviation of 300 g. The mean gestational age of the babies was 31.83 ± 1.86 weeks in study group and 31.82 ± 1.70 weeks in 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 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 (83.3%), lethargy (90%), hypothermia (50%), apnoea (73.3%), abdominal distension (66.6%), bleeding tendency (50%), jaundice (43.3%) and respiratory distress (16.7%). Statistical test showed that the two groups were identical in respect of clinical presentation (Table 2). Complete blood culture revealed about (73.3%) of the cases were positive while 26.7% are negative in study group. Among the control group the positive cases are (70%) and negative are (30%). CRP was found high among 70% of both study and control groups.

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

Of the 43 culture-positive neonates, 97.8% had Gram-negative bacilli, only 1 (2.2%) had Gram-positive. *Klebsiella pneumoniae* was the most common organism (53.3%, 24/45), followed by *Acinetobacter* (24.5%, 11/45) and *pseudomonas* (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 cephalosporin, ciprofloxacin and imipenem were mostly sensitive to all the isolates. In more than half of the cases netilmicin and gentamicin was also found sensitive. 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. t-test was done and statistically significant changes were found in all three immunoglobulin levels after treatment with IVIG (p<0.0001) (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 ± 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 ± 6.88 days with minimum of 3 days (1 patient discharged after 3 days on risk bond) and maximum 35 days. This difference between the two groups was found to be statistically significant (t=2.6, p<0.05). Out of total 60 patients in both groups, 46 (76.7%) were released from the hospital when they were cured. The mortality rate was lower in study group but the difference between the two groups was not statistically significant (c^2= 3.35, p=0.06).

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
Dyspnoea	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
Diarrhoea	02 (06.6)	01 (03.3)	p>0.05

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)

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)

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>0.05). The clinical presentation of our patients in Table 2 is reliable to those found in other comparative studies and in addition described in the standard paediatric text books [13-17]. In developed nations, Group B *Streptococcus* and coagulase negative *Staphylococci* are the most widely recognized etiological agents for ahead of early and late onset of neonatal sepsis respectively. Be that as it may, in developing countries these organisms are uncommon with an altogether unique bacterial range; *Escherichia coli* and *Klebsiella* are the most well-known organisms bringing on neonatal septicaemia [1]. This thought is turned out to be valid if there should be an occurrence of the present study and different studies done in the developing countries [18,19]. In the present study, *Klebsiella* was observed to be most regular organism bringing on sepsis in study (56.5%) and control (50%), which was trailed by *Pseudomonas* 21.8% and 27.2% in study and control groups separately. there was no development of Group B *Streptococcus* and *Staphylococcus* was discovered just in one case. In one study directed in a similar NICU in 2013,

almost three fourths (73%) of the detached organisms from blood in neonatal septicaemia were Gram-negative bacilli. Nevertheless, *Escherichia coli* was then the most well-known organism took after by *Klebsiella pneumoniae* (23%) and *Pseudomonas* (10%). Among the Gram-positive organisms. *Staphylococcus aureus* was found in 16.7% of the isolates [20]. Such momentous change in isolation pattern from same facility two years apart might be because of the way that aetiology of neonatal septicaemia may change inside a topographical area with time [21-24]. Because of this, intermittent reconnaissance for specialists of disease and their anti-infection affectability profiles is prescribed. Distinctive reviews done in India likewise indicated Gram-negative organisms were transcendent reason for neonatal sepsis [14,18]. In the blood of preterm neonates, contrasted and full term, the IgG level is lower during childbirth and declines all the more quickly to a lower fixation. 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 [25]. Since IgM and IgA are impermeable to placental obstruction; their levels during childbirth are low when contrasted with grown-up levels. Large amounts of IgM and IgA in the present review could be because of sub-clinical intrauterine contamination or because of neonatal disease after birth [26]. In a review by Fischer, et al. the mean IgG levels in untimely neonates was 368 mg/dl during childbirth, declined to 104 mg/dl at 3 months of age and afterward gradually increased [10]. In their review, Weisman, et al. watched noteworthy increment ($p<0.05$) of serum IgG in IVIG treated patients [27]. Kinney, et al. likewise observed that mean IgG levels got before each resulting dosage were altogether higher in IVIG treated neonates than in the placebo treatment arrangements ($p<0.05$) [28]. In another review on "IVIG treatment for early onset sepsis in untimely newborn children", Weisman, et al. revealed that in patients with early-onset sepsis, add up to serum levels of IgG were essentially expanded after infusion with IVIG in correlation with albumin [29]. While in our study group it was found to be 621 mg/dl. The perception with respect to the length of facility stay is like some other vast planned studies directed at various centres. Conway in his study revealed that the infants in treatment group had lesser stay in ICU ($p=0.001$) [25]. Lassiter detailed that administration of IVIG was related with a reduced stay of hospitalization [11]. In another randomized review led by Kinney, et al. the mean term of facility stay remain for patients getting IVIG was 43.1 days (36.3-49.9), which was 46.5 days (39-54) for placebo treatment group [28]. However, in another multi centre randomized review in Hyderabad, India, the scientists discovered almost no distinction in length of hospital study among the three groups: 18.3 ± 2.34 days in placebo treatment, 17 ± 2.08 days in IVIG bunch and 13.3 ± 2.91 days among the control group [9]. The death rate was much lower in the gathering treated with IVIG (13.3%) in contrast with the control group (33.3%). In spite of the fact that the distinction in mortality between the two gatherings was not measurably huge ($c^2=3.35$, $p=0.06$), but rather the inclination demonstrates that the death rate was much lower in the study group. The reviews directed at various hospitals at various periods demonstrates a blended outcome if there should be an occurrence of lessening of death rate in IVIG treated neonates experiencing neonatal sepsis. Sidiropoulos was the main examiner to report the utilization of IVIG to treat set up bacterial sepsis barbaric neonates [30]. In his review the occurrence of death was 27% (4/15) in controls and 10% (2/20) in the IVIG beneficiaries ($p=0.016$). IVIG treatment had all the earmarks of being best when managed to septic neonates of low birth weight. Consolidating the four reviews intended to survey the helpful adequacy of IVIG uncovered that passing happened in 9% (6/67) of IVIG beneficiaries, contrasted and 30% (20/67) of control [10]. Weisman, et al. in their review revealed that there were 29.41% deaths (5/17) in control patients against 11.76% deaths (2/14) in IVIG treated untimely neonates [29]. The death rate was equivalent (17.5%) in both groups of untimely neonates in another study [31]. In another multicentre study in Hyderabad, India, the mortality was additionally observed to be same (28%) in three groups, placebo treatment, IVIG and control [9]. Haque, et al. in their two studies inferred that the mortality from sepsis is fundamentally lower in the IVIG treated groups ($p<0.001$) [32,33].

CONCLUSION

From the findings of the present study it can be concluded that the IVIG is a useful adjunct for the antibacterial defenses in newborn infants with septicaemia.

Limitations: However, the safety and long-term consequences of administering IVIG to newborn premature infants are yet to be defined.

REFERENCES

[1] Kuruvilla, K. A., et al. "Neonatal group B streptococcal bacteraemia in India: ten years' experience." *Acta paediatrica* 88.9 (1999): 1031-1032.
[2] Haque, Khalid N. "Infection and immunity in the newborn." *Forfar and Arneill's textbook of paediatrics*. 5th ed. London: Churchill Livingstone, 1998. 273-89. Print.
[3] Koutouby, Ayman, and Javed Habibullah. "Neonatal sepsis in Dubai, United Arab Emirates." *Journal of tropical pediatrics* 41.3 (1995): 177-180.
[4] Kim, Kwang Sik. "Use of intravenous immunoglobulin in the treatment of neonatal sepsis." *American Journal of Diseases of Children* 143.11 (1989): 1257-1258.
[5] Lacy, J. B., and Ohlsson, A. "Administration of intravenous immunoglobulins for prophylaxis or treatment of infection in preterm infants: meta-analyses." *Archives of Disease in Childhood-Fetal and Neonatal Edition* 72.3 (1995): F151-F155.
[6] Whitelaw, A. "Treatment of sepsis with IgG in very low birthweight infants." *Archives of disease in childhood* 65.4 Spec No (1990): 347.
[7] Ohlsson, A., and Lacy, J. B. "Intravenous immunoglobulin for preventing infection in preterm and/or low-birth-weight infants." *The Cochrane Library* (2001).
[8] Ramasubramanian, K. V., et al. "The role of intravenous immunoglobulins in pediatric diseases." (1999).
[9] Shenoi, Arvind, et al. "Multicenter randomized placebo controlled trial of therapy with intravenous immunoglobulin in decreasing mortality due to neonatal sepsis." *Indian Pediatr* 36.11 (1999): 1113-8.
[10] Fischer, G. W. "Use of intravenous immune globulin in newborn infants." *Clinical and experimental immunology* 97. Suppl 1 (1994): 73.
[11] Lassiter, H. A. "Intravenous immunoglobulin in the prevention and treatment of neonatal bacterial sepsis." *Advances in pediatrics* 39 (1991): 71-99.
[12] Ballard, J. L., et al. "New Ballard Score, expanded to include extremely premature infants." *The Journal of pediatrics* 119.3 (1991): 417-423.
[13] Haque, M. M., et al. "Clinical manifestation and bacteriological profile of Septicaemia in preterm Neonates: Experience from a tertiary level pediatric hospital." *Bangladesh Journal of Medical Science* 10 (2004): 29-33.
[14] Chandna, Anita, et al. "Rapid diagnostic tests in neonatal septicaemia." *Indian journal of pediatrics* 55.6 (1988): 947-953.
[15] Mir, F., Aman, S., and Raza Khan, S. "Neonatal sepsis: A review with a study of 50 cases." *Journal of tropical pediatrics* 33.3 (1987): 131-5.
[16] Haque, K. N., Remo, C., and Bahakim, H. "Comparison of two types of intravenous immunoglobulins in the treatment of neonatal sepsis." *Clinical and experimental immunology* 101.2 (1995): 328.
[17] Gotoff, S. "Infections of the neonatal infant." *Nelson Textbook of Paediatrics*. 16th ed. Philadelphia: WB Saunders Company, 2000. 538-52. Print.
[18] Rao, P. Sugandhi, Meera Baliga, and Shivananda, P. G. "Bacteriology of neonatal septicaemia in a rural referral hospital in South India." *Journal of tropical pediatrics* 39.4 (1993): 230-233.
[19] Aurangzeb, Brekhna, and Abdul Hameed. "Neonatal sepsis in hospital-born babies: Bacterial isolates and antibiotic susceptibility patterns." *Journal of the College of Physicians and Surgeons-Pakistan: JCPSP* 13.11 (2003): 629-632.
[20] Ahmed, A. S. M. N. U., et al. "Clinical and bacteriological profile of neonatal septicaemia in a tertiary level pediatric hospital in Bangladesh." *Indian pediatrics* 39.11 (2002): 1034-1038.
[21] Dawodu, A., Al Umran, K., and Twum-Danso, K. "A case control study of neonatal sepsis: Experience from Saudi Arabia." *Journal of tropical pediatrics* 43.2 (1997): 84-88.
[22] Moreno, MarÍa Teresa, et al. "Neonatal sepsis and meningitis in a developing Latin American country." *The Pediatric infectious disease journal* 13.6 (1994): 516-520.
[23] Saha, S. K., et al. "The increasing burden of disease in Bangladeshi children due to Haemophilus influenzae type b meningitis." *Annals of tropical paediatrics* 17.1 (1997): 5-8.
[24] Gladstone, Igor M., et al. "A ten-year review of neonatal sepsis and comparison with the previous fifty-year experience." *The Pediatric infectious disease journal* 9.11 (1990): 819-890.
[25] Conway, S. P., Gillies, D. R. and Docherty, A. "Neonatal infection in premature infants and use of human immunoglobulin." *Archives of disease in childhood* 62.12 (1987): 1252-1256.
[26] Tejavej, Anant, Chutima Anantachai, and Phaiboolya Phanichyakarn. "Immunoglobulins in maternal and umbilical cord blood of Thais." *The Southeast Asian journal of tropical medicine and public health* 14.3 (1983): 345-348.
[27] Weisman, Leonard E., et al. "Intravenous immune globulin prophylaxis of late-onset sepsis in premature neonates." *The Journal of pediatrics* 125.6 (1994): 922-930.

[28] Kinney, Janet, et al. "Efficacy and pharmacokinetics of intravenous immune globulin administration to high-risk neonates." *American Journal of Diseases of Children* 145.11 (1991): 1233-1238.
[29] Weisman, Leonard E., et al. "Intravenous immune globulin therapy for early-onset sepsis in premature neonates." *The Journal of pediatrics* 121.3 (1992): 434-443.
[30] Sidiropoulos, D., et al. "Immunoglobulin substitution in the treatment of neonatal septicemia." *Schweizerische Medizinische Wochenschrift* 111.44 (1981): 1649-1655.
[31] Stabile, A., et al. "Intravenous immunoglobulin for prophylaxis of neonatal sepsis in premature infants." *Archives of disease in childhood* 63.4 (1988): 441-443.
[32] Haque, Khalid N., et al. "Intravenous immunoglobulin for prevention of sepsis in preterm and low birth weight infants." *The Pediatric Infectious Disease Journal* 5.6 (1986): 622-625.
[33] Haque, Khalid N., Muzamil H. Zaidi, and Hasan Bahakim. "IgM-enriched intravenous immunoglobulin therapy in neonatal sepsis." *American Journal of Diseases of Children* 142.12 (1988): 1293-1296.