

Role of Immunotherapy (IVIg) in the Treatment of Neonatal Sepsis

Reza Saeidi, MD¹ Ahmad Shah Farhat, MD^{2*} Ashraf Mohammadzadeh, MD³
Mahbobeh Gholami, MSc⁴

1- Neonatal Research Center, school of medicine, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran

2,3- Neonatal Research Center, school of medicine, Emam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran

4- Midwifery master, Department of midwifery, Neyshabur Branch, Islamic Azad University, Neyshabur, Iran

Abstract

Objectives

This study sought to evaluate the effect of intravenous immunoglobulin (IVIg) in neonatal sepsis in preterm babies.

Methods

This clinical trial was done at the NICU of Imam Reza Hospital in Mashhad (Iran) from September 2006 to September 2007. We used a dosage regimen of 1g/kg/day. In this study we had 50 patients with documented sepsis; 25 of them received antibiotics (controls) and 25 of them received antibiotic and IVIg as adjuvant therapy. Finally we compared the outcomes of both groups.

Results

In this study all septic newborns had positive blood cultures. The most common cause of sepsis in our study was klebsiella (56% of control and 36% of case groups). In both groups we found 62% early onset sepsis. There was no statistically significant difference between mortality rate in two groups (52% VS 48% of case and control, $P > 0.05$).

Conclusion

This study did not find any significant decrease in mortality rate with IVIg therapy in neonatal sepsis.

Keywords

Neonate, preterm, sepsis, IVIg

Introduction

Despite the advances in neonatal care, neonatal sepsis remains a major cause of mortality and morbidity in the newborn and 1.6 million neonates die every year from infection.⁽¹⁻⁴⁾

IgM is not trans-placental transferred and maternal IgG transfer starts around 30 weeks of gestation to reach maternal levels at term.⁽⁵⁾ Hence the preterm infant is antibody deficient and this immune deficient state is worsened in sepsis.⁽⁶⁾ The aim of treatment in severe infection is to kill the pathogens with antibiotics, control the hemodynamic impairment and organ dysfunction.⁽⁷⁾ Recently, the International Sepsis Campaign published evidence-based guidelines for the treatment of sepsis. They indicated therapeutic modalities which are

effective and which are not. The guidelines state that polyclonal IVIGG therapy has been reported to reduce mortality rates in sepsis and are a promising therapeutic tool but asserted that there is insufficient evidence to suggest a robust conclusion of benefit.⁽⁷⁾ The exact mode of action of IVIg is not clearly understood.⁽⁵⁾

Commercially available polyclonal (IVIg) preparations contain over 96% IgG, containing a broad spectrum of opsonic and neutralizing antibodies aimed at a variety of organisms⁽⁸⁾. The World Health Organization has set minimum standards required of commercially available IVIg preparations. They include a minimal plasma donor pool of at least 1000.⁽⁵⁾ Infused IVIg has a half-life of about 7 to 14 days in the newborn infant.⁽⁴⁾ IVIg has the ability to neutralize

Correspondence *: Ahmad Shah Farhat, Neonatal Research Center NICU, Imam Reza Hospital, Mashhad- Iran

Tel: (+98) 511 8521121 Mobile: (+98) 9153146917 Fax: (+98) 5118525316 Email: farhata@mums.ac.ir

bacterial toxins, modulate the production of pro and anti-inflammatory cytokines, chemokines and expression of adhesion molecules.⁽⁸⁻¹⁰⁾

Recently however, El-Nawawy et al have shown significant reduction in mortality, length of stay in intensive care in infants with sepsis syndrome treated with IVIG.⁽¹¹⁾ Alejandria suggested that IVIG lowers mortality in severe sepsis in adults.⁽¹²⁾ Intravenous immunoglobulin has been used to treat and prevent neonatal sepsis since 1980 but its use still remains controversial.^(13, 14)

Though IVIG was first used in neonatal sepsis over a quarter of a century ago many clinicians still view IVIG therapy as either experimental or not evidence-based. To improve the outcome from neonatal sepsis we will need not only to kill the pathogen but also modulate the immune system. Based on the evidence, immunomodulation with intravenous immunoglobulin in the management of neonatal sepsis is worth serious consideration. Hence this study designed to evaluation the effect of intravenous immunoglobulin (IVIG) in neonatal sepsis.

Methods

This randomized clinical trial single blind study was done at the NICU of Imam Reza Hospital in Mashhad from September 2006 to September 2007. Sample size was determined with 95% confidence interval in 50 patients. There were 25 patients in case group and 25 patients in the control group. The study group was prescribed IVIG plus antibiotics and only antibiotics in controls. We used a single dosage regimen of 1g/kg/day. Data were collected with a questionnaire and a check list. Infants with gestational age less than 37 weeks, birth weight less than 2500g,

with sepsis diagnosis (positive blood culture) and hospitalized at the NICU were included in this study.

Exclusion criteria were congenital malformation, IUGR/ SGA, CPR upon delivery, low APGAR (<5), sever asphyxia, intraventricular hemorrhage, necrotizing enterocolitis, and neonates from addicted mothers. Finally data was analyzed with SPSS11.5 and chi-square tests.

Results

From September 2006 to September 2007, 50 patients were (25 in study and 25 in controls) with no gender differences (male 50%, female 50%) of neonates were enrolled. In case group there was no significant difference between 2 groups (p=0.25). There was no significant difference in gestational age between 2 groups (p=0.999, Table 1).

The birth weight of the study group was 1350g with a standard deviation of 12 g and control group neonates were 1520 g with a standard deviation of 300 g. The mean gestational age of the babies was 32.90 ± 1.60 weeks in study group and 31.8 ± 2.3 weeks in controls.

The mean age on admission was 6.2 ± 4.1 days and 5.3 ± 3.2 days in the study and control groups respectively. There was no significant difference between the groups in birth weight, gestational age or age (P>0.05,). There was no significant difference between two groups in leucocyte count (P=0.812), neutrophil count (P=0.371), platelet count (P=0.400) or CRP (p=0.040). Neutropenia was present in 12.5% of control and 0 in the study group.

The predominant organisms causing neonatal

Table 1. Age at sepsis onset

Day	Groups				Total	
	Control		Case		Number	%
	Number	%	Number	%		
0-7	18	72%	18	72%	36	72%
8-28	7	28%	7	28%	14	28%
Total	25	100%	25	100%	50	100%

Chi-Square: X² = 0.0 df = 1 P = 0.999 (NS)

sepsis in our NICU were klebsiella (56% of control vs. 36% of case groups) then E.Coli (12% vs. 4%) and acinetobacter (12% vs. 4%). Finally there was no statistically significant difference between mortality rates in both groups (P=0.999, Table 2).

Discussion

In this study, we did not find significant decrease in mortality in those who received IVIG in addition to the standard treatment (52% mortality rate in case group versus 48% in controls). There was no statistically significant difference in gestational age, birth weight and early or late onset sepsis. This is in view of the fact that not only is the outcome unaltered but also the mean duration of hospital stay was similar in the (IVIG) and control groups.

El-Nawawy et al have shown significant reduction in mortality, length of stay in intensive care and complications in infants with sepsis syndrome treated with (IVIG).⁽¹¹⁾ Alejandria suggested that IVIG lowers mortality in severe sepsis in adults.⁽¹²⁾ Intravenous immunoglobulin has been used to treat and prevent neonatal sepsis since 1980 but its use still remains controversial.^(13, 14)

Though (IVIG) was first used in neonatal sepsis over a quarter of a century ago many clinicians still view (IVIG) therapy as either experimental or not evidence-based.^(12, 16, 17)

Six studies (n = 318) which reported mortality showed statistically significant reduction in infants with suspected sepsis given IVIG (RR 0.63, 95% CI – 0.40-1.00).⁽¹⁸⁾

Treatment with (IVIG) in seven trials (n=262) of cases of subsequently proven infection resulted in a statistically significant reduction in mortality

following IVIG therapy (RR 0.55, 95% CI – 0.31- 0.98, NNT 11).⁽¹⁸⁻²⁰⁾ Mathur et al showed a significant decrease in mortality in preterm neonates.⁽⁷⁾ Although the number of studies are few and the total number of patients studied small but all the studies reviewed clearly show that the use of (IVIG) reduces mortality from neonatal sepsis significantly.⁽⁵⁾ Thus, (IVIG) as adjuvant therapy offers a significant advantage over conventional therapy in sepsis. But Friedman et al showed no statistically significant difference.⁽⁶⁾ A multicentre placebo controlled trial by Weisman et al showed significant decrease in mortality in the 1st 7 days, while the survival at 56 days had not improved significantly.⁽¹²⁾ And In our study, we did not find any significant decrease in mortality in (IVIG) group. Of course this study concluded that there is no role of intravenous immunoglobulin (single dose not multiple dose) in the treatment of definite neonatal sepsis. We suggest, a larger sample size study, with multiple dose of (IVIG), in preterm septic newborns, to affirm the role of IVIG. From the finding of the present study single dose IVIG therapy in preterm infants with positive blood culture is not useful.

Conclusion

It is concluded that there is no role of intravenous immunoglobulin (single dose) in the treatment of neonatal sepsis; but we suggest, a larger study sample, with multiple dose therapy, in term and preterm septic newborns, to affirm the role of (IVIG) more confidently.

Acknowledgement

We are grateful to Mrs. Zahra Ahmadi and the

Table 2. Mortality rate

Mortality	Groups				Total	
	Control		Case		Number	%
	Number	%	Number	%		
Mortality rate	12	48%	13	52%	25	50%
Total	25	100%	25	100%	50	100%
Chi-square :	X2 = 0.0		df = 1		P = 0.999 (NS)	

research department of Mashhad University of Medical Sciences for their help.

References

1. Ahmed SS, Chowdhry M, Huque MM, Begum D, Ahmed A. Role of Intravenous Immunoglobulin (IVIG) as an adjuvant in the treatment of neonatal sepsis in preterm babies. *J of Bangladesh College Of Physician & surgeons*. 2006; 24(930):97-104.
2. Mandhir S, Lauren H, Carmella MA, Mitchell C. Immunotherapy in the prophylaxis and treatment of neonatal sepsis. *Current opinion in Pediatrics*. 2003; 15(2):155-160.
3. Stoll BJ, Hansen N. Infections in VLBW infants: Studies from NICHD. *Neonatal Network Seminars in Perinatology*. 2003; 27: 293-301.
4. Haque KN: Neonatal Infections. In: *Textbook of Paediatrics*. Eds. McIntosh, Stenson B. 6th Edition. Churchill Livingstone: Edinburgh: 2004; 759-764.
5. Haque KN. Immuno-modulation in neonatal sepsis: intravenous immunoglobulin therapy in the prevention and the treatment of neonatal sepsis. *Haematologica reports*. 2006; 2(100):38-41.
6. Janeway C, Travers P, Capro J et al. The humoral immune response. In: Janeway C, Travers P, Capro J, Walport M (eds), *Immunology, the immune system in health and disease*. 4th Edition. Churchill, Livingstone: New York :1999; 307-360.
7. Dellinger RP, Carlet JM, Masur H et al. Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. *Critical Care Med*. 2004; 32: 858-873.
8. Loulthon L, Kaver SV, Spalter SH et al. Mechanism of action of intravenous immunoglobulin in immune mediated disease. *Clin Exp Immunol*. 1996; 104 (Suppl 1): 3-9.
9. Basta M, Fries LF, Frank MM: High dose IVIG inhibits in vitro uptake of C4 fragments onto sensitized erythrocytes. *Blood*. 1991; 77: 376-380.
10. Dembinski J, Martini R, Behrendt D, Bartman P. Modification of cord blood IL-6 production with IgM-enriched human immunoglobulin in term and preterm infants. *Cytokine*. 2004; 26:25-29.
11. El-Nawawy A, El-Kinany H, El-Sayed MH, Boshra N. Intravenous Polyclonal Immunoglobulin administration to sepsis syndrome patients: A prospective Study in a paediatric intensive care unit. *J Trop Paediatrics*. 2005; 25: 1-8.
12. Alejandria MM, Lansang MA, Dans LF, Mantaring BV. Intravenous Immunoglobulin for treating sepsis and septic shock. *Cochrane Systemic Review*. 2001. CD 001090.
13. Haque KN, Zaidi MH, Haque SK et al. Intravenous Immunoglobulin for prevention of sepsis in preterm and low birth weight infants. *Paed Infec Dis J*. 1986; 5: 622-625.
14. Sidiropoulos D, Bhome U, von Muralt G et al. Immunoglobulin supplementation in prevention or treatment of neonatal sepsis. *Paed Infec Dis J*. 1986; 5: 193 –194.
15. Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. *Cochrane Systemic Review* 1998, issue 4. Updated 2004. CD 001239.
16. Jenson HB, Pollock BH. Meta-analysis of the effectiveness of intravenous immunoglobulin for the prevention and treatment of neonatal sepsis. *Seminars in Perinatology* 1998; 22: 50-63.
17. Haque KN. Should Intravenous Immunoglobulin be used in the treatment of neonatal sepsis? *Br J Intensive Care* 1997; 7: 12-16.
18. Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. *Cochrane Systemic Review* 1998, issue 4. Updated 2004. CD 001239.
19. Haque KN, Remo C, BaHakim H. Comparison of two types of intravenous immunoglobulin in the treatment of neonatal sepsis. *Clin Exp Immunol*. 1995; 101:328-333.
20. Samatha S, Jalalu MP, Hegde RK et al. Role of IgM enriched IVIG as adjuvant to antibiotics in neonatal sepsis. *Karnataka Paediatrics* 1997; 11: 1-6.