Intravenous immunoglobulin in ABO and Rh hemolytic diseases of newborn

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ABSTRACT

Objective: To evaluate whether the use of intravenous immunoglobulin in newborn infants with isoimmune hemolytic jaundice due to Rh and ABO incompatibility is an effective treatment in reducing the need for exchange transfusion.

Methods: This study included all direct Coombs' test positive Rh and ABO isoimmunized babies, who admitted in the Neonatal Intensive Care Unit of Ghaem Hospital of Mashhad University of Medical Sciences, Iran, from October 2003 to October 2004. Significant hyperbilirubinemia was defined as rising by ≥0.5 mg/dl per hour. Babies were randomly assigned to received phototherapy with intravenous immunoglobulin (IVIg) 0.5 g/kg over 4 hours, every 12 hours for 3 doses (study group) or phototherapy alone (control group). Exchange transfusion was performed in any group if serum bilirubin exceeded ≥20mg/dl or rose by ≥1mg/dl/h.

Results: A total of 34 babies were eligible for this study (17 babies in each group). The number of exchange transfusion, duration of phototherapy and hospitalization days, were significant shorter in the study group versus control group. When we analyzed the outcome results in ABO and Rh hemolytic disease separately, the efficacy of IVIg was significantly better in Rh versus ABO isoimmunization. Late anemia was more common in the IVIg group 11.8% versus 0%, p=0.48. Adverse effects were not observed during IVIg administration.

Conclusion: Administration of IVIg to newborns with significant hyperbilirubinemia due to Rh hemolytic disease reduced the need for exchange transfusion but in ABO hemolytic disease there was no significant difference between IVIg and double surface blue light phototherapy.

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Hemolytic disease of newborn due to blood group incompatibility is an important cause of hyperbilirubinemia with significant morbidity in the neonatal period.[1] The degree to which the fetus is affected correlated with the amount of maternal antibody that crosses the placenta.[2] Exchange transfusion and phototherapy have traditionally been used to treat jaundice and avoid the associated neurological complications. Exchange transfusion is not without risk and intravenous immunoglobulin (IVIg) has been suggested as an alternative therapy for isoimmune hemolytic jaundice to reduce the need for exchange transfusion.[3,4] Intravenous immunoglobulin has been used previously in immunological neonatal disorders including alloimmune and autoimmune neonatal thrombocytopenia and in preterm and low birth weight infants as an adjuvant therapy in neonatal sepsis.[5,6] But, there are controversies about the optimum dose of IVIg, the most efficacious number of infusions, and the best preparation. In addition, IVIg therapy has been reported in hyperbilirubinemia of Rh hemolytic disease, its use in ABO hemolytic disease has been reported in only a few studies.[7] This study was carried out to determine that, by using multiple dose of IVIg, we could decrease the need for exchange transfusion in ABO and Rh hemolytic diseases of newborns.

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Methods. This case control prospective study was performed at the Neonatal Intensive Care Unit (NICU) of Ghaem Hospital of Mashhad University of Medical Sciences, Iran, over a period of one year from October 2003 to October 2004. The study population included 34 babies with ABO or Rh incompatibility. Inclusion criteria were 1) Gestational age ≥ 37 weeks. 2) Positive direct Coomb's test in Rh and ABO incompatible neonates. 4) Significant hyperbilirubinemia was defined as rising by ≥0.5 mg/dl per hour. 5) Bilirubin levels below the exchange transfusion criterion on admission. 6) There was not other risk factors such as sepsis, glucose-6-phosphate dehydrogenase (G6PD) deficiency that could rise bilirubin. Babies were randomly assigned into 2 groups. Study group received double surface blue light phototherapy plus IVIg 500 mg/kg body weight within 2-4 hours of admission for 3-consequence doses each 12 hours. Control group received double surface blue light phototherapy alone. Phototherapy was started once the baby was admitted to NICU. Exchange transfusion was carried out in each group if at any time the bilirubin level reached ≥20 mg/dl, or rose by 1 mg/dl/h. All babies were adequately hydrated and fed with breast milk. Patients were closely monitored for possible side effects of IVIg, by observation of change in respiration rate and pattern, body temperature, heart rate and blood pressure .The blood groups of mothers and babies were recorded. Complete blood count, hematocrit, reticulocyte, G6PD level were performed in all babies. Bilirubin level was measured every 6 hour. Gender, birth weight, the type of incompatibility and the postnatal age were recorded when the therapy was started. We followed babies in the outpatient clinic at the age of 2 and 4 and 6 weeks to check their hemoglobin and reticulocyte count for development of late anemia. Hemoglobin <120 g/l was defined to be late anemia and transfusion was carried out when hemoglobin level was <70 g/l. The study protocol was approved by the Local Ethics Committee and informed consent was obtained from parents before randomization.

The results were analyzed using the Statistical Package for Social Sciences (SPSS 11.5) program and expressed as mean and standard deviation. x^2 and t-student tests were employed to test whether there was a statistically significant difference between the groups. Differences at the level of $p<0.05$ were considered to be statistically significant.

Results. A total of 34 babies were eligible for this study, 17 babies received IVIg and 17 babies received only the standard treatment. There were no significant differences between the 2 groups with respect to birth weight, postnatal age, gender, the initial values of serum bilirubin, hematocrit, reticulocyte count and the number of cases with ABO or Rh hemolytic disease (**Table 1**). According to blood group incompatibility, 21 (62%) of the 34 babies had ABO hemolytic disease (12 babies with blood group A, 9 babies with blood group B and all mothers were of the O blood group), and 13 (38%) had Rh isoimmunization. Three (17.6%) babies in the study group required exchange transfusions compared to 11 (64.7%) babies in the control group (p=0.005). In addition, we found a significant difference in duration of phototherapy (p=0.01) and hospitalization

Table 1 - Clinical and laboratory data for both groups.

Clinical laboratory	Study group	Control group	*P* value
Birth weight (g)	2636 ± 254	2731 ± 327	0.28
Gender (M/F)	8/9	6/11	-
Postnatal age (hour)	22.76 ± 8.8	17.58 ± 9.71	0.11
Bilirubin (mg/dl)	14.2 ± 2.71	15.5± 3.83	0.76
Hematocrit level (%)	43.2 ± 5.67	42.51 ± 8.2	0.76
ABO incompatibility (%)	11 (64.7)	10 (58.8%)	0.72
Rh incompatibility (%)	6 (35.3)	7 (41.2%)	0.87
Retic count (%)	3.36 ± 1.76	3.97 ± 2.01	0.37

Table 2 - Comparison of results in both groups.

Results	Study group	Control group	*P* value	95% Confidence intervals
Exchange transfusion (%)	3 (17.6)	11 (64.7)	0.005	-
Mean number of exchange transfusion per patient (range)	0.17± 0.39 (0-1)	1.11 ± 0.99 (0-3)	0.001	-1.46, -0.41
Duration of phototherapy in days (range)	4.94 ± 0.96 (4-6)	6.41± 2.00 (4-11)	0.01	-2.41, -0.28
Duration of Hospitalization in days (range)	6 ± 1 (5-8)	7.41± 2.09 (4-11)	0.017	-2.35, -0.11
Late anemia (%)	2 (11.8)	-	0.48	-

days (p<0.017) between the study and control groups (**Table 2**). The mean time at which the first dose of IVIg was given in Rh incompatible babies 19.66 ± 8.11 (range 10 –32) hours and in ABO incompatible babies 24.4 ± 9.14 (range 12- 44) hours. When followed for late anemia, 2 (11.8%) babies in the study group had anemia and required blood transfusion. We analyzed the outcome results in Rh and ABO hemolytic disease separately. Among the infants with Rh hemolytic disease the number of babies who had exchange transfusion, duration of phototherapy and hospitalization days, were significantly less in the study than control group (**Table 3**). However, for the infants with ABO hemolytic disease, 2 (18.2%) babies in the study group and 4 (40%) in the control group required exchange transfusions (p=0.36). Also there were no significant differences in duration of phototherapy and hospitalization days between the study and control groups in these babies (**Table 4**). No immediate adverse effects related to the IVIg administration were recorded, including fever allergic reactions, hemolysis or volume overload.

Discussion. With widespread use of anti-D immunoglobulin prophylaxis in preventing sensitization of Rh negative mothers, the incidence of Rh hemolytic disease of newborn has fallen dramatically. Other blood group incompatibilities such as ABO hemolytic disease is still an important cause of significant hyperbilirubinemia, which may necessitate exchange transfusion.[7] In recent years, it has been shown that IVIg has been effective and less invasive than exchange transfusion in the treatment of neonatal hemolytic jaundice due to blood group incompatibility.[8,9] In the study by Rubo et al,[10] 32 infants with Rh hemolytic disease were randomly assigned to receive phototherapy with IVIg and phototherapy alone. The IVIg group required significantly lesser number of exchange transfusion than the control group.[10] Although IVIg has been shown to reduce the need for exchange transfusion in Rh hemolytic disease, but the clinical efficacy of IVIg in ABO isoimmunization has been reported in only a few studies. Ergas et al[11] treated 9 babies with ABO hemolytic disease in the first 72 hours of life with IVIg (1g/kg). In 7 of 9 babies the risk of hyperbilirubinemia was attenuated and exchange transfusion was not required following treatment with IVIg.[11] In the study by Miqdad et al,[7] administration of IVIg to newborns with significant hyperbilirubinemia due to ABO hemolytic disease with positive direct Coomb's test reduced the need for exchange transfusion and duration of phototherapy. In our study, the efficacy of IVIg was significantly better in Rh versus ABO isoimmunization. This is explained by the fact that the mechanism by which IVIg reduces the degree of hemolysis is by blocking the reticuloendothelial Fc receptor sites and hence

Table 3 - Results in Rh incompatibility.

Incompatibility	Study group n=6	Control group n=7	*P* value	95% Confidence intervals
Exchange transfusion (%)	1 (16.7)	7 (100)	0.005	-
Mean number of exchange transfusion per patient (range)	0.16 ± 0.4 (0-1)	2 ± 0.57 (1-3)	<0.0001	-2.45; -1.21
Duration of phototherapy in days (range)	5.33 ± 1.03 (4-6)	7.14 ± 1.57 (4-9)	0.035	-3.46; -0.15
Duration of Hospitalization in days	5.66 ±0.88 (5-7)	8.28 ± 1.70 (5-10)	0.006	-4.30; -0.93
Late anemia (%)	1 (16.7)	-	0.46	-

Table 4 - Results in ABO incompatibility.

Results in ABO	Study group n=11	Control group n=10	*P* value	95% confidence interval
Exchange transfusion (%)	2 (18.2)	4 (40)	0.36	-
Mean number of exchange transfusion per patient (range)	0.18 ± 0.4 (0-1)	0.5 ± 0.7 (0-2)	0.21	-0.83; 0.2
Duration of phototherapy in days (range)	4.72 ± 0.9 (4-6)	5.9 ± 2.18 (4-11)	0.11	-2.67; 0.32
Duration of hospitalization in days (range)	6.18 ± 1.07 (5-8)	6.8 ± 2.2 (4-11)	0.41	-2.17; 0.94
Late anemia (%)	1 (9.1)	-	0.5	-

preventing the extravascular destruction of neonatal red blood cell by transplacentally acquired maternal isoantibodies. In Rh hemolytic disease the surface of red blood cells become coated with antibodies but this is in contradistinction to ABO hemolytic disease where are the sparse distribution of A and B sites on the red cells.[12] Although IVIG is effective in the treatment of hyperbilirubinemia due to hemolytic disease of newborn, its effect is variable. The admission time of cases, severity of hemolysis and dose of IVIg may influence the results. Mukhopadhyay et al[13] used 2 dose of IVIg in 34 Rh isoimmunized babies. In their study IVIg was effective in decreasing the mean maximum bilirubin levels and the need for repeated exchange transfusion, however it did not alter the duration of phototherapy. It should be due to delay in initiation of the treatment with IVIg.[13] Tanyer et al[14] investigated the effect of multiple doses versus single dose IVIg therapy in babies who had ABO and Rh hemolytic disease. In their study, babies that received multiple dose of IVIg (0.5g/kg) daily for 3 days, required no exchange transfusion versus 12% in the group that received only single dose of IVIg and 33% in the control group. Although, they did not analyze the outcome result according to ABO or Rh incompatibility separately.[14] In our study, we used 3 dose of IVIg (0.5g/kg) every 12 hours as soon as the diagnosis of hemolytic anemia is made because delay in IVIg administration decreases successful treatment. Transfusion for late anemia have been reported when hemolytic disease of newborn is treated with IVIg in addition to phototherapy because the antibody has not been washed out.[10] In this study late anemia that required packed red cell transfusion were seen in 2 babies in the IVIg group. One of the beneficial effects of using IVIg in the treatment of hemolytic disease of newborn is the reduction in duration of hospital stay. In our study, the length of hospitalization was significantly shortened in the IVIg group compared with the control group. The financial saving from the shortened stay and duration of phototherapy offsets the cost of IVIg. Intravenous immunoglobulin considered being a relatively safe product, but it is not without risk of adverse reactions. Mild adverse effects are fever, allergic reaction, hemolysis, transient hypotension and fluid over load. Serious adverse effects are rare and include anaphylaxis and possible transmission of infections. To reduce the risk of transmission of infective agents, donors and donations are selected and plasma pools are tested and undergo a viral partitioning and inactivation process. With improvement in this processing the serious adverse effects will be avoided.[15]

We conclude that IVIg is an effective therapy for reducing the need for exchange transfusion in Rh hemolytic disease of newborn but it needs more studies to get license for routine use in the other forms of hemolytic disease of newborn such as ABO isoimmunization

References

1. Zipursky A, Bowman JM. Isoimmune Hemolytic Disease. In: Nathan OG, Oski FA, editors. Hematology of Infancy and Childhood, 4th ed. Philadelphia: WB Saunders C; 1993.p. 66-69.
2. Koenig JM. Evaluation and Treatment of Erythroblastosis Fetalis in the Neonate. In: Christensen RD, editor. Hematologic Problems of the Neonate. 1st ed. Philadelphia: W B Saunders; 2000. p. 185-203.
3. Alcock GS, Liley H. Immunoglobulin infusion for isoimmune hemolytic jaundice in neonates. ***Cochrane Database Syst Rev*** 2002; 3: CD 003313.
4. Jackson JC. Adverse Events Associated With Transfusion in Healthy and ill Newborns. ***Pediatrics*** 1997; 99: E7.
5. Ouwehand WH, Smith G, Ranasinghe E. Management of severe alloimmune thrombocytopenia in the newborn. ***Arch Dis Child Fetal Neonatal Ed*** 2000; 82: 173-175.
6. Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. ***Cochrane Database Syst Rev*** 2000; 2: CD001239.
7. Miqdad AM, Abdelbasit OB, Shaheed MM, Seidahmed MZ, Abomelha AM, Arcala OP. Intravenous immunoglobulin G (IVIG) therapy for significant hyperbilirubinemia in ABO hemolytic disease of the newborn. ***J Maternal Fetal Neonatal Med*** 2004; 16: 163-166.
8. Maisels MJ, Baltz RD, Bhutani VK, Newman TB. Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. ***Pediatrics*** 2004; 114: 297-316.
9. Sato K, Hara T, Kondo T, Iwao H, Honda S. High dose intravenous gammaglobulin therapy for neonatal immune hemolytic jaundice due to blood group incompatibility. ***Acta Paediatr Scand*** 1991; 80: 163-166.
10. Rubo J, Albrecht K, Lasch P, Laufkotter E, Leititis J, Marsan D, et al. High Dose Intravenous Immunoglobulin Therapy for hyperbilirubinemia Caused by Rh Hemolytic Disease. ***J Pediatr*** 1992; 121: 93-97.
11. Ergaz Z, Arad I. Intravenous Immunoglobulin Therapy in Neonatal Immune Hemolytic Jaundice. ***J Perinatal Med*** 1993; 21: 183-187.
12. Gottstein RS, Cooke RW. Systemic Review of Intravenous Immune Globulin in Hemolytic Disease of the Newborn. ***Arch Dis Child, Fetal Neonatal Ed*** 2003; 88: F6-10.
13. Mukhopadhyay K, Murki S, Narang A, Dutta S. Intravenous Immunoglobulins in Rhesus Hemolytic Disease. ***Indian J Pediatr*** 2003; 70: 697-699.
14. Tanyer G, Siklaer Z, Dallar Y, Yildimak Y, Tiras U. Multiple Dose IVIG Treatment in Neonatal Immune Hemolytic Jaundice. ***J Trop Pediatr*** 2001; 47: 50-53.
15. Yap PL. Intravenous Immunoglobulin and Hepatitis C Virus: An Overview of transmission episodes with emphasis on manufacturing data. ***Clin Ther*** 1996; 18 Suppl B: 43-58.