PROPHYLACTIC INTRAVENOUS IMMUNOGLOBULIN IN NEONATAL IMMUNE HEMOLYTIC JAUNDICE

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ABSTRACT

Background: Evidence indicating that intravenous immunoglobulin (IVIG) could prove effective against neonatal immune hemolytic hyperbilirubinemia, reducing the need for exchange transfusion.

Objective: To determine the prophylactic effect of IVIG in decreasing the incidence and severity of neonatal immune hemolytic jaundice.

Methods: A case-control prospective randomized trial in Hafez and Nemazi Hospitals in Shiraz, Iran, was undertaken between September 1998 through August 1999. Fulfilling the inclusion criteria forty full-term, healthy neonates with Rh or ABO incompatibility, entered the study and were randomly assigned into 2 equal groups. IVIG was administered in a single dose of 500 mg/kg to 20 neonates in the treatment group 4-6 hours during the first 24 hours of life. Nothing was given to 20 controls. All neonates were evaluated prospectively to detect jaundice or pallor till 10-days-old.

Results: The IVIG-treated neonates had a smaller rise in their bilirubin levels, required significantly less phototherapy (9% vs. 35%) (p<0.05) and a shorter duration of hospitalization than those in the control group. In both groups, the hematocrit and hemoglobin values remained fairly stable and none of the infants had bilirubin levels exceeding the exchange levels. No side effects of IVIG were seen.

Conclusions: Our results indicate that IVIG administration may be effective in prevention of neonatal immune hemolytic hyperbilirubinemia. However, further studies are required to validate the efficacy of this treatment and to determine the optimal dose, number of infusions and the best preparation of IVIG treatment.


Key Words • Hemolysis • immunoglobulins, intravenous • jaundice

Introduction

The clinical significance of hyperbilirubinemia in neonates lies in its association with kernicterus, where bilirubin appears to cause damage to the central nervous system.1

One of the most common causes of hyperbilirubinemia is immune hemolytic jaundice in the newborn. Maternal IgG antibodies, usually reacting against fetal ABO- or Rh incompatible RBCs, may cross the placenta, enter the fetal circulation, and cause hemolysis, anemia and hyperbilirubinemia.2 Current recommendations for treatment include phototherapy and exchange transfusion, however, there are serious clinical problems associated with exchange transfusion that may reach as high as 4.2%.3

In recent years, several reports have indicated that the severity of neonatal immune hemolytic hyperbilirubinemia may be ameliorated by high-dose IVIG, reducing the need for exchange transfusion.3-12

The rationale for this treatment is based on the assumed similarity between the destructive immune mechanisms observed in immune hemolytic jaundice (antibody-sensitized erythrocytes) and neonatal immune thrombocytopenia (antibody-sensitized platelets), and on the beneficial therapeutic effect of high-dose IVIG treatment reported in the latter disease should be taken into consideration.4

IVIG has been widely used in a variety of pediatric conditions, and complications are rare. The risks of therapy are almost certainly less than the risk of exchange transfusion.1

We performed a randomized controlled trial to determine the prophylactic effect of IVIG in decreasing
the incidence and severity of neonatal immune hemolytic jaundice.

**Materials and Methods**

**Study Population:**

This case-control prospective randomized trial was undertaken at Hafez and Nemazi Hospitals affiliated to the Shiraz University of Medical Sciences between September 1998 through August 1999. The subjects were selected considering inclusion and exclusion criteria as follows:

**Inclusion Criteria:**

a) Rh positive neonates  
b) History of Rh positive sibling(s)  
c) O type maternal blood group  
d) Positive direct Coomb’s test (DCT)  
Both A and B in Rh negative mothers.

**Exclusion Criteria:**

a) Rh negative neonates  
b). Other causes of hemolysis and hyperbilirubinemia  
c) Family history of hemolytic disorder (for example: G6PD deficiency)  
d) Birth weight < 2500 grams  
e) Birth injury, asphyxia  
f) History of intrauterine infections  
g) Extensive bruising or hematoma

Out of 1,593 newborns, 40 full-term, healthy neonates fulfilled the inclusion criteria and entered the study after the informed consent had been obtained from the parents following a detailed explanation about the nature and reason of the study.

**Study Protocol:**

The cord blood was tested for blood group (BG), Rh, DCT, plasma bilirubin, hemoglobin, and HCT. Information regarding the birth weight, gestational age, APGAR score (1 and 5 min), maternal indirect Coombs’ test (ICT), maternal age, number of the pregnancies and their intervals, mode of delivery, family history of hemolytic disorders, intrauterine infections, jaundiced sibling(s), and Rhogam injections were also taken into consideration.

The neonates were randomly assigned into treatment and control groups. The study was not blinded due to the lack of an appropriate placebo. Twenty neonates made up the treatment and the remaining 20 the control groups.

**Administration of IVIG:**

In the treatment group, the neonates received 3% solution of IVIG (30 mg/ml) in normal saline (Sandoglobulin, Sandoz, Germany) as a single dose of 500 mg/kg body weight (? 17 ml/kg) in 4-6 hours during the first 24 hours of life.
All children were closely monitored for any possible side effects of IVIG therapy, including changes in heart rate and blood pressure. Nothing was given to the 20 controls. Further therapy was identical for the treatment and control groups.

**Follow-up:**

The neonates were evaluated for the presence of jaundice or pallor by physical examination and also serial bilirubin, Hb, and HCT were determined on the 1\textsuperscript{st}, 3\textsuperscript{rd}, 5\textsuperscript{th}, 7\textsuperscript{th}, and 10\textsuperscript{th} days of life.

The following parameters were analyzed:

a) Increase in bilirubin level.
b) Decrease in hemoglobin, and hematocrit.
c) Number of babies who received photo-therapy.
d) Duration of phototherapy.
e) Frequency of need to exchange or blood transfusion.
f) Duration of hospitalization.
g) Side effects of IVIG.

**Conventional therapy:**

The indications for phototherapy and exchange transfusion were based on postnatal age (hours), birth weight and the level of bilirubin.\(^1\)

**Laboratory Methods:**

Serum total bilirubin levels were determined with Reichert-Jung Unistat Bilirubinometer, and with Toitu Bilirubin meter BL-200 (Technicon, Saint-Denis, France).

Direct bilirubin levels were determined with Reichert-Jung Unistat Bilirubinometer using a modified diazo reaction, and with Technicon RA-1000 (Technicon, Saint-Denis, France).

Hemoglobin and hematocrit were checked with Coulter Electronics Ltd, Automated Hematology Analyser and with Technicon H. 1\textsuperscript{TM} system (Technicon, Saint-Denis, France).

G6PD was checked with G6PD fluorescent spot test (Kimia Pajouhan Co., Tehran).

Blood group and Rh were determined with Anti-A, Anti B and Anti-D (the Blood Transfusion Service of Iran, Shiraz) using test tube for neonates and test slide for mothers.

DCT and ICT were checked with anti-human globulin serum and bovine albumin solution (the Blood Transfusion Service of Iran, Shiraz).

**Statistical Analysis:**

The results were analyzed for statistical significance by means of Fisher exact test. (An expected cell value was less than 5) Comparisons between control and treatment groups were performed with t-test for equality of means, Levene’s test for equality of variances, \(X^2\)-test for equality of ratios, and by the Mann-Whitney u-test.
Results

Baseline Characteristics:

There were no statistically significant differences between the treatment and control groups with respect to the mean gestational age, birth weight, gravida number of mother, gravida interval, delivery mode, mother’s age, APGAR score (1 and 5 min), and sex distribution.

In addition, no significant differences between the two groups were observed in regard to the cord blood hemoglobin, hematocrit, and serum bilirubin concentrations at birth, with HCT and Hb remaining fairly stable. None of the neonates developed clinical jaundice in the first 24 hours of life.

Thirty seven neonates (19 from the treatment and 18 from the control groups) were Rh- and the remaining 3 (1 in the treatment and 2 in the control groups) ABO-incompatibles.

None of the infants had bilirubin levels exceeding the exchange levels, probably at least in part, due to close follow-up during the study period and early detection of hyperbilirubinemia and management with phototherapy.

Effect of IVIG on Jaundice and Hemolysis:

The increase in bilirubin levels during the first 10 days of life was significantly lower in IVIG-treated neonates than the control group (1-tailed P=0.004).

IVIG treated neonates needed virtually no phototherapy when compared to the controls (0% vs. 35%) (2-tailed P=0.008).

The neonates (7 from the control group) required a mean of 4 day course of phototherapy (Range:2-6 days).

Of these neonates requiring phototherapy, 6 were Rh- and 1 ABO-incompatibles. These differences were significant comparing to the respective Rh- and ABO-incompatibles of the treatment group. (Fisher exact test: 1-tailed P-value: 0.007, 2-tailed P-value: 0.007, respectively.).

Neonates treated with IVIG also showed shorter duration of hospitalization. No side effects of IVIG therapy were observed.

Table 1 shows the distribution of the maternal and baby blood groups of the jaundiced neonates.

Discussion

Initial reports of IVIG use for Rh isoimmunization described the reduction of maternal antibody titers and severity of fetal hemolysis following the administration of massive doses of IVIG to Rh sensitized mothers.13 Although the mechanism of action remains unclear, the proposed explanations are feed-back inhibition of antibody synthesis, competition for macrophage or Fc receptors of target cells and blockade of Fc mediated antibody placental transport.3,7,10,12-17 High dose IVIG has also been recommended by some, in the neonatal period.3-11

Our decision to give high dose IVIG therapy to the affected newborn infants was based on the
consideration that hyperbilirubinemia in both Rh and ABO sensitized infants results from the destruction of neonatal red cells which have been coated by transplacentally acquired maternal isoantibody causing extravascular erythrocyte destruction, probably mediated by Fc receptor bearing cells within the reticuloendothelial system.

IVIG therapy may alter the course of immune hemolytic disease by blocking Fc receptors, resulting in inhibition of hemolysis and subsequent reduction of bilirubin formation. However, this proposed mechanism is yet to be proved.\textsuperscript{3,6-8,10,11} If this is the case, IVIG should be administered as soon as possible after birth, to reduce the degree of hemolysis and hyperbilirubinemia.\textsuperscript{3,7}

The difference of our study with previous studies lies in using IVIG as a preventive measure, before any significant hyperbilirubinemia could develop.

The definitive therapy for rhesus hemolytic disease is prevention of the disease itself. This is achieved by the widespread usage of anti-D immunoglobulin (Rhogam).

Any treatment capable of replacing exchange transfusions should be welcomed and indeed high-dose IVIG offers this possibility.\textsuperscript{3}

In this study, no side effects of IVIG therapy were observed which correlates with previous reports.\textsuperscript{3,6,10,11} Administration of IVIG therapy is less invasive and also less expensive than exchange transfusion, characteristics that make IVIG highly valuable in developing countries, and particularly in regions with limited resources of personnel and sophisticated equipment.\textsuperscript{3,7,18,19}

\textbf{Conclusion}

The data presented suggests that prophylactic IVIG can decrease the incidence and severity of neonatal immune hemolytic jaundice. However, there is a need for further studies to establish the optimal dose, number of infusions, and preparation of IVIG.

\textbf{References}


