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ORIGINAL ARTICLE

Intravenous Immunoglobulin G Treatment in ABO Hemolytic Disease of the Newborn, is it Myth or Real?

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Abstract Intravenous Immunoglobulin G (IVIG) therapy has been used as a component of the treatment of hemolytic disease of the newborn. There is still no consensus on its use in ABO hemolytic disease of the newborn routinely. The aim of this study is to determine whether administration of IVIG to newborns with ABO incompatibility is necessary. One hundred and seventeen patients with ABO hemolytic disease and positive Coombs test were enrolled into the study. The subjects were healthy except jaundice. Infants were divided into two groups: Group I (n = 71) received one dose of IVIG (1 g/kg) and LED phototherapy whereas Group II (n = 46) received only LED phototherapy. One patient received erythrocyte transfusion in Group I, no exchange transfusion was performed in both groups. Mean duration of phototherapy was 3.1 ± 1.3 days in Group I and 2.27 ± 0.7 days in Group II ($p < 0.05$). Mean duration of hospital stay was 5.34 ± 2.2 days in Group I and 3.53 ± 1.3 days in Group II ($p < 0.05$). Mean duration of phototherapy was 4.0 ± 1.5 days and 2.73 ± 1.1 days in double and single doses of IVIG respectively, and this was statistically significant ($p < 0.05$). IVIG therapy didn't decrease neither phototherapy nor hospitalization duration in infants with ABO hemolytic disease. Meticulus follow-up of infants with ABO hemolytic disease and LED phototherapy decreases morbidity. IVIG failed to show preventing hemolysis in ABO hemolytic disease.

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Introduction

Blood group incompatibility induced hemolytic jaundice can cause significant morbidity and mortality in the newborn period [1]. Hemolysis from ABO incompatibility is one of the most common cause of isoimmune hemolytic disease during neonatal period. Infants with blood group type A or B, carried by blood group type O mother, will have a positive antibody because of maternal anti-A or anti-B transfer into the fetal circulation. Ten percent of these infants will present with hemolytic disease [2]. Most of the infants presents with unconjugated hyperbilirubinemia in the first 24 h of life and it is rarely a cause in patients who are discharged from nursery and readmit with severe hyperbilirubinemia [3]. Hyperbilirubinemia is defined as total bilirubin above 95th percentile on the hour specific Bhutani nomogram [4]. Appropriate intervention is important to prevent long term neurologic sequelae such as kernicterus in every infant with ABO hemolytic disease. Once hyperbilirubinemia has been detected prompt therapy should be initiated. Phototherapy is the most widely used treatment in patients with unconjugated hyperbilirubinemia.

Intravenous Immunoglobulin G (IVIG) therapy has been widely used for a variety of indications in newborn period such as alloimmune neonatal thrombocytopenia and an adjunctive treatment of neonatal infections. American Academy of Pediatrics, recommends high dose IVIG (0.5–1 g/kg) as an additional treatment of Rh and ABO hemolytic disease and its use however there is no consensus on its routine use in ABO hemolytic disease yet [4]. IVIG is thought to decrease hemolysis by blocking Fc receptor sites

of reticuloendothelial cells preventing lysis of neonatal erythrocytes [5]. This competitive inhibition can suggest that, early administration of IVIG is necessary in immune hemolytic diseases of newborn. However there are still debates on routine IVIG use in ABO hemolytic disease of the newborn. In this study we evaluated the effect of IVIG treatment on infants with ABO hemolytic disease.

Methods

We performed a retrospective study of 117 term infants with ABO hemolytic disease with direct antiglobulin test (DAT) that were followed in our NICU between 2006 and 2011. The subjects were healthy except jaundice. Patients with prematurity, G6PD deficiency, sepsis were not enrolled into the study. Clinical and laboratory data including birth weight, gestational age, maternal and infant blood type, age at admission (day), hemoglobulin level and reticulocyte count, need for exchange and/or erythrocyte transfusion, phototherapy duration, and hospitalization duration, were collected retrospectively from patients medical records.

Infants were investigated as two groups. Group I (n = 71) received IVIG (1 g/kg) and LED phototherapy whereas Group II (n = 46) received only LED phototherapy alone.

Phototherapy was provided with light-emitting diodes (LED) phototherapy system (Natus Medical Inc., San carlos, CA, USA, intensity. 30 μW/cm^2/nm, spectrum 450–470). Every patient received LED phototherapy treatment soon after admission to the NICU regardless of IVIG therapy. And phototherapy was stopped when the bilirubin levels decreased to safe limits defined in American Academy of Pediatrics criteria.

In group I IVIG treatment was started together with the phototherapy in patients with anemia or high reticulocyte count or severe hemolysis. Anemia was described as hemoglobulin level below 14 g/dL; high reticulocyte count was described as above 7 % on the first day, above 3 % between second and fourth day and above 1 % by 7 days of life; and severe hemolysis was diagnosed on peripheral smear as spherocytes, polychromasia and increased number of nucleated red blood cells [6]. Possible side effects of IVIG was also noted.

Comparisons between groups were made by Student t Test and Mann–Whitney U Test. $p < 0.05$ was considered to be significant. All statistical analysis were carried out on a personal computer with a software Statistical Package for Social Sciences (SPSS for Windows© version 15).

Results

A total of 117 neonates who met the inclusion criteria were enrolled into the study. 71 neonates (Group I) received IVIG treatment combined with phototherapy; of these infants 9 infants received two doses of IVIG when the hemolysis was thought to be going on after the first dose. 46 neonates (Group II) received only phototherapy during their hospitalization. All neonates received LED phototherapy immediately after the admission to the NICU. All mothers had O blood type; 88 infants (75.2 %) had A blood group and 29 infants (24.8 %) had B blood group. when groups were compared, there were no significant difference in gestational age, birth weight, admission age and first month hemoglobulin level. Demographic data is shown on Table 1.

Mean duration of phototherapy was 3.1 ± 1.3 days in Group I and 2.27 ± 0.7 days in Group II, and this was statistically significant ($p < 0.05$) (Table 1). Mean duration of hospital stay was 5.34 ± 2.2 days in Group I and 3.53 ± 1.3 days in Group II, and this was statistically significant ($p < 0.05$) (Table 1).

In Group I, only one patient received erythrocyte suspension, in Group II none of the patients had transfusion. In both groups none of the patients needed exchange transfusion.

In Group I, 9 patients received double dose of IVIG, when single and double dose IVIG receivers are compared; mean phototherapy duration was 4.0 ± 1.5 days in patients who received double dose and 2.73 ± 1.1 days in patients who received single dose, and this was statistically significant ($p < 0.05$). However there were no significant difference in gestational age, birth weight, admission age, duration of hospital stay and first month hemoglobulin level when single or double doses of IVIG receivers are compared (Data not shown).

No adverse effects of IVIG including anaphylaxis, hypersensitivity, thrombosis, pulmonary emboli, renal insufficiency and aseptic meningitis was noted.

Table 1 Characteristics and comparision of infants are shown

	Group I IVIG and phototherapy ($n = 71$)	Group II phototherapy alone ($n = 46$)	p
Gestational age	38.5 ± 0.4	38.5 ± 0.6	ns
Birth weight (grams)	3,348 ± 394	3,312 ± 393	ns
Age on admission (day)	1.9 ± 0.9	2.2 ± 1.4	ns
Duration of phototherapy (day)	3.18 ± 1.3	2.27 ± 0.7	**<0.05**
Duration of hospital stay (day)	5.34 ± 2.2	3.53 ± 1.3	**<0.05**
Hb level on first month	11.1 ± 1.0	11.0 ± 1.4	ns

ns not significant

Discussion

ABO hemolytic disease is an important cause of unconjugated hyperbilirubinemia in neonates requiring phototherapy and hospitalization especially after the advances in the management of rhesus hemolytic disease. Neonatal jaundice is four times higher in patients with positive DAT when compared with negative DAT in ABO hemolytic disease [7]. Early screening, close follow-up, and prompt treatment is necessary in ABO hemolytic disease of newborn. When total bilirubin exceeds 95th percentile on the hour specific Bhutani nomogram phototherapy should be started immediately. Although prophylactic phototherapy was found to be effective in decreasing bilirubin level in the first 48 h of life, it did not result in a sustained clinical benefit so phototherapy is recommended as a rescue therapy rather than prophylactic treatment [8].

IVIG has been used for the treatment of alloimmune thrombocytopenia and neonatal infections [9, 10]. It is also widely used in rhesus hemolytic disease of the newborn as an alternative therapy to avoid exchange transfusion [4, 11]. Alpay et al. [12] showed that, high dose of IVIG (1 g/kg) reduces hemolysis, serum bilirubin levels and risk of exchange transfusion in rhesus and ABO hemolytic disease on the other hand; Girish et al. [13] demonstrated that, low dose of IVIG (0.5 g/kg) was also found to be as efficacious as high dose IVIG in reducing the duration of phototherapy. However low dose IVIG found to be less effective in avoiding exchange transfusion in rhesus hemolytic disease of the newborn [14]. Apart from these results, Smits-Wintjen concluded that prophylactic treatment with IVIG in rhesus hemolytic disease did not reduce the need for exchange transfusion or adverse neonatal outcomes [15]. Most of these studies were done in patients with rhesus hemolytic disease of the newborn, there are small number of patients with ABO hemolytic disease, it is not clear that IVIG is efficacious in ABO hemolytic disease of newborns so routine use of IVIG is still controversial because its efficacy has not been definitely demonstrated. In a prospective study Migdad et al. randomised 112 term neonates with ABO hemolytic disease with positive DAT. First group received phototherapy plus IVIG (0.5 g/kg) and the second group received phototherapy alone. They concluded that IVIG reduces the need for exchange transfusion in ABO hemolytic disease of the newborn [16]. In a retrospective study Demirel et al. [17] found out that IVIG therapy (single or multiple) did not affect exchange transfusion, need of erythrocyte transfusion and hospitalization time when combined with LED phototherapy in ABO hemolytic disease of the newborn.

In our study, Group I had longer phototherapy duration and longer hospital stay. IVIG was given in patients with high reticulocyte counts or with anemia (hemoglobulin level below 14 mg/dL) on admission or severe hemolysis diagnosed on peripheral smear. Longer phototherapy duration and longer hospital stay might be the result of ongoing hemolysis, however IVIG seems to be not very efficacious on preventing hemolysis in ABO hemolytic disease. Also patients who received the second dose of IVIG had longer duration of phototherapy, these patients had uncontrolled hemolysis and IVIG do not seem to prevent this severe hemolysis.

Only one patient had erythrocyte transfusion, this patient had severe hemolysis and required two doses of IVIG. No patient had exchange transfusion in our study population, this might be probably due to close follow-up, early screening, and prompt LED phototherapy.

Phototherapy seems to have the key role in these patients. High intensity phototherapy (spectral irradiance higher than 30 $\mu W/cm^2/nm$, 430–490 nm band) delivered as close as infants surface is effective in reducing serum unconjugated bilirubin levels and need for exchange transfusion [4]. When compared with conventional phototherapy, LED lights are more effective in reducing serum unconjugated bilirubin levels [18]. In our study all patients were treated with LEDs, low rates of erythrocyte transfusion and no need for exchange transfusions might be due to this new advanced phototherapy method regardless of IVIG.

It is shown that IVIG therapy is not preventing hemolysis and LEDs are effective in reducing unconjugated bilirubin levels in ABO hemolytic disease of the newborn. We recommend LED phototherapy as the initial therapy to treat hyperbilirubinemia in ABO hemolytic disease of the newborn. IVIG administration should be thought if serum bilirubin level is close to exchange transfusion level in spite of LED phototherapy. Since our study is retrospective, randomised controlled studies are needed to study the effect of IVIG in ABO hemolytic disease.

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