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Original article

High dose intravenous immunoglobulin in Rh and ABO hemolytic disease of Egyptian neonates

Background: *Despite advances made in the use of phototherapy, and in order to avoid sequelae of kernicterus, the treatment of hyperbilirubinemia may require one or several exchange transfusions, an invasive therapy which is not without risk. Intravenous immune globulin treatment in isoimmune hyperbilirubinemia has been shown to be effective, but the response to treatment is variable.* ***Objective:*** *To evaluate effectiveness of high dose Intravenous immune globulin (HD-IVIG) in reducing the need for exchange transfusion, duration of phototherapy and/or hospitalization in neonates with isoimmune hemolytic disease due to Rh or ABO incompatibility.* ***Methods:*** *The study included 116 direct Coombs' test positive neonates delivered at Gynecology and Obstetrics Hospital of Ain Shams University, Cairo, Egypt. They were randomly assigned to receive phototherapy with HD-IVIG in a single dose of 1 gm/kg (60 neonates, intervention group) or phototherapy (56 neonates, control group).* ***Results:*** *Nine neonates in the intervention group (15%) and 23 (41%) in the control group required single exchange transfusion (p< 0.001). Multiple exchange transfusion was indicated in 15 neonates (26.8%) in the control group versus none in the intervention group (p< 0.001). Compared with control group, neonates in the intervention group had shorter mean duration of intensive phototherapy (9.97 versus 35.5 hours, p<0.001) and hospital stay (27.9 versus 103.5 hours, p< 0.001). No adverse effects of HD-IVIG administration were noted.* ***Conclusion:*** *HD-IVIG effectively reduced the requirement for exchange transfusion and duration of phototherapy and hospitalization in isoimmune hemolytic disease of the newborn.*

Key words: Hemolytic disease of newborn, hyperbilirubinemia, exchange transfusion, high dose intravenous immunoglobulin.

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INTRODUCTION

Hemolytic disease of the newborn (HDN) due to red cell alloimmunisation is an important cause of hyperbilirubinemia with significant morbidity in the neonatal period.[1,2] Hemolytic disease of the newborn has unfortunately continued to contribute to perinatal and neonatal morbidity and mortality in developing countries.[3] Traditional neonatal treatment of HDN consists of intensive phototherapy and exchange transfusion (ET). However, ET is a high-risk invasive procedure associated with a significant rate of adverse effects. Although the mortality rate associated with ET is currently reported to be <0.3% in term infants, the morbidity rates can reach 74% and includes catheter-related complications, sepsis, thrombo-cytopenia, and hypocalcemia.[4-10] Neonatal treatment with intravenous immunoglobulin (IVIG) has been suggested as an alternative therapy to ET for rhesus HDN.[11-13] Recommendations for the routine use of IVIG are controversial because of various methodological limitations of the studies.[14-17]

The aim of our study was to evaluate whether the use of high dose intravenous immunoglobulin (HD-IVIG) with intensive phototherapy in neonates with isoimmune hemolytic disease due to RH or ABO incompatibility could be effective in reducing the need for ET and duration of both phototherapy and hospital stay.

METHODS

Patients

The present study is a prospective randomized controlled trial, conducted in the neonatal intensive care unit (NICU) at Gynecology and Obstetrics Hospital, Ain Shams University over 28 months. The study included 116 neonates. Inclusion criteria: gestational age e32 weeks, body weight e2 kg, positive direct Coombs' test in presence of ABO or Rh incompatibility, serum total bilirubin level indicative for phototherapy and below exchange

transfusion criteria, and a reticulocyte count e10%. Exclusion criteria: perinatal asphyxia, congenital malformation, severe respiratory distress, sepsis during hospital stay or metabolic problems. The study was approved by the faculty ethical committee and a verbal informed parental consent was obtained. A total of 116 neonates were included; 62 full term and 54 preterm neonates[18] with proven isoimmune hemolytic anemia due to Rh (n= 20) or ABO (n=96) incompatibility.

Study design

On study entry, infants were assigned to the IVIG treatment (intervention group) or placebo (control group). The method of treatment allocation was simple using coin tossing by the principal investigator for each trial participant. Phototherapy and exchange transfusion were performed according to the latest AAP guidelines[11]. All eligible neonates were admitted to NICU and received conventional intensive phototherapy using a white light with an intensity of 20 µW/cm/nm given by air shield and Ohmeda lamps, in combination with blue light of 30 µW/cm/nm.

During phototherapy, extra fluids (10 mL/kg) were administered. In the intervention group, patients received conventional intensive phototherapy plus IVIG (supplied by Green Cross of South Korea) as a single dose of 1 gm/kg (administered within 1-4 hours of admission, over 2 hours). Patients were closely monitored for possible side effects of IVIG as hypotension, tachycardia, or allergic reactions.

Whenever indicated, exchange transfusion was performed with double-volume transfusion (160 mL/kg) using irradiated and leukocyte-depleted compatible erythrocytes.

During hospital stay, neonates were assessed for serum total and direct bilirubin levels every 6 hours, and 24 hours post discharge, and daily for hemoglobin, reticulocyte, C-reactive protein.

Follow up Hb level was measured at age of 1 and 2 months. The primary outcome was the number of exchange transfusions per neonate. Secondary outcomes were duration of phototherapy and hospital stay.

Statistics

Data were reported as means and standard deviations, or as numbers and percentages, as appropriate. Statistical analysis was performed with SPSS 17.0 (SPSS Inc, Chicago, IL). The Student *t* test and Mann-Whitney test were used for continuous variables. Chi and Fisher's exact tests were used for categorical variables, as appropriate. A *p* value of <0.05 was considered statistically significant.

RESULTS

Our study included a total of 116 neonates; 62 full term and 54 preterm neonates: categorized as 20 with Rh isoimmune hemolytic disease and 96 with ABO incompatibility. There were a total of 62 with blood group A and 34 neonates with blood group B, distributed between the two groups.

There were no statistically significant differences between the two groups with respect to age, birth weight, and initial values of total serum bilirubin, hemoglobin, or reticulocyte count (table 1). The rate of decline in total serum bilirubin was significantly higher among those who received HD-IVIG (table 2). No immediate adverse effects related to IVIG were noted, including fever, allergic reactions, volume overload or hemolysis.

As for the primary outcome, the number of those who acquired serum bilirubin levels indicative of ET (once or multiple) was less in the intervention group. The same was observed for both duration of phototherapy and hospitalization (tables 3 and 4).

Reticulocyte count dropped significantly after 24 hours of phototherapy from 11.4±1.3 to 5.9±1.9% in the intervention group as compared to a decline from 11.1±2.1 to 6.9±2.9, in the control group ($p < 0.05$).

Results were uniform across the different subgroups; whether preterm or full-term neonates, and with ABO or Rh incompatibility, with significant differences when intervention group was compared to control group with respect to outcomes of treatment (tables 5 and 6).

When followed up for late anemia, none of the neonates in either group required top-up blood transfusion, and individual hemoglobin levels remained above 10 gm/dl (table 7).

Table 1. Initial characteristics of both groups at study entry

	Intervention group (N=60) mean ±SD	Control group (N=56) mean ±SD	P
Gestational age (weeks)	36.6±2.9	35.6±2.9	0.07
Birth weight (kg)	3.0±0.46	2.7±0.50	2.1
Full term/Preterm, no (%)	38/22	24/32	0.9
Male gender, n (%)	27(45)	34(60.7)	0.89
Age at admission (hrs)	51.5±25.4	57.8±	0.01
Age at management (hrs),	54.3±24.9	57.8±	0.01
Initial Hemoglobin (gm/dl)	13.97±1.4	13.77±1.2	0.4
Reticulocyte count (%)	11.4±1.3	11±2.1	0.27
Total serum bilirubin (mg/dl)	16.1±4.6	16.97±3.8	0.07

Table 2. Rate of decrement of mean total serum bilirubin from baseline in the studied groups

	Intervention group (N=60) mean ±SD	Control group (N=56) mean ±SD	P
Initial total serum bilirubin (mg/dl)	16.1±4.6	16.97±3.8	0.07
Total serum bilirubin after 6 hrs	13.9±4.6	17.1±3.3	< 0.001
Total serum bilirubin after 12 hrs	12.9±5.2	17.4±3.3	< 0.001
Total serum bilirubin after 18 hrs	11.9±5.1	16.9±3.4	< 0.001

Table 3. Outcomes of treatment in intervention versus control group

	Intervention group (N=60)	Control group (N=56)	P
Single Exchange transfusion, n (%)	9 (15)	23 (41)	< 0.001
Multiple exchange transfusion, n (%)	0	15 (26.8)	< 0.001**
Duration of hospitalization (hrs) mean +SD	27.9±18.7	103.5±30.8	< 0.001
Duration of intensive phototherapy (hrs) mean +SD	9.97±6.2	35.5±27.3	< 0.001*

* Mann-Whitney test; **Fisher's exact test

Table 4. Percentage distribution of neonates who required exchange transfusion in subgroups

Subgroups	Intervention group (N=60)	Control group (N=56)	P
Rh incompatibility (N=20)	3/12 (25%)	8/8 (100%)	<0.001*
ABO incompatibility (N=96)	6/48 (12.5%)	30/48 (62.5%)	<0.001
Full term (N= 62)	6/38 (15.8%)	16/24 (66.7%)	>0.05
Preterm (N=54)	3/22 (13.6%)	22/32 (68.8%)	<0.001*

*Fisher's exact test

Table 5. Outcomes of treatment in Rh and ABO incompatibility subgroups

Outcomes	Rh in intervention group (n=12)	Rh in control group (n=8)	P	ABO in intervention group (n=48)	ABO in control group (n=48)	P
Gestational age mean±SD	36.4±3.1	35.5±3.3	0.53	36.7±2.8	36.2±2.9	0.42
Birth weight mean±SD	2.9±0.6	2.8±0.7	0.72	2.9±0.5	2.7±0.45	0.037
Single Exchange transfusion, n (%)	3 (25%)	7 (87.5%)	<0.001*	6 (12.5%)	16 (33.3%)	<0.01**
Multiple exchange transfusion, n (%)	0	3 (37.5%)	<0.01*	0	12 (25%)	<0.001**
Duration of hospitalization (hrs) mean±SD	25±18.1	99±35.6	<0.001*	28.6±18.9	104.3±30.2	<0.001
Duration of intensive physiotherapy (hrs) mean±SD	11.5±9.4	38.3±28.9	<0.001*	9.6±5.2	35±27.3	<0.001*

* Mann-Whitney test; **Fisher's exact test

Table 6. Outcomes of treatment in full term and preterm subgroups

Outcomes	Full term in intervention group (n=38)	Full term in control group (n=24)	P	Preterm in intervention group (n=22)	Preterm in control group (n=32)	P
Gestational age	38.6±1.1	38.8±0.9	0.34	33.2±1.1	33.2±0.8	0.89
Birth weight	3.2±0.3	3.2±0.2	0.78	2.3±0.2	2.3±0.14	0.24
Single Exchange transfusion, n (%)	6 (15.8%)	10 (41.6%)	<0.05*	3 (13.6%)	13 (40.6%)	<0.05**
Multiple exchange transfusion, n (%)	0	6 (25%)	<0.01*	0	9 (28.1%)	<0.01**

Table 7. Serial mean Hemoglobin levels during the study period

Variables	Intervention (n) mean ±SD	Control (n) mean ±SD	P
Hb (gm/dl) at Hour 12	(60) 13.976±1.382	(56)13.784±1.242	0.437
Hb (gm/dl) at Hour 24	(60) 13.813±1.365	(55)14.024±1.996	0.42
Hb (gm/dl) at Hour 36	(36) 13.972±1.187	(52)14.348±1.105	0.248
Hb (gm/dl) at Hour 48	(27) 14.256±0.686	(46)14.317±1.166	0.831
Hb (gm/dl) at age of one month	(60) 13.365±1.647	(56)14.232±1.373	0.019
Hb (gm/dl) at age of two months	(60) 11.818±1.783	(56)12.330±1.828	0.13

DISCUSSION

The mainstay of treatment of isoimmune hemolytic disease is intensive phototherapy with exchange transfusion if the total serum bilirubin despite of phototherapy, still approaches a level considered to cause a risk of bilirubin encephalopathy. Neonatal treatment with intravenous immunoglobulin (IVIG) has been suggested as an alternative therapy to exchange transfusion for HDN.

With the wide use of anti-D to prevent Rh hemolytic disease, other blood group incompatibilities now assume a major role in the causation of neonatal hyperbilirubinemia which may require exchange transfusion[19, 20]. Hence, over 28 months, we were able to include only 20 neonates with Rh but good number of ABO incompatibility (96) which shows that ABO hemolytic disease is an important cause of significant hyperbilirubinemia in Egyptian neonates. Our study is the only randomized controlled trial to date to include full and preterm neonates and both Rh and ABO incompatibility. Our results support the recommendation of the American Academy of Pediatrics and many other studies to give IVIG in rhesus and ABO isoimmune hemolytic disease.[11,16,21-23] Our study results showed that administering IVIG has resulted in significantly fewer neonates requiring exchange transfusion compared to those who received phototherapy alone. The significant reduction in the need for exchange transfusion was consistent among different subgroups; Rh and ABO incompatibility, and full term and preterm neonates. The mechanism by which IVIG is thought to reduce the degree of hemolysis is by blocking the reticuloendothelial FC receptor sites and hence preventing the extravascular destruction of neonatal red blood cells by transplacentally acquired maternal antibodies.[15] This competitive action of IVIG with isoantibodies has led to the suggestion that, in order for IVIG to be effective it must be administered as soon as the diagnosis of isoimmune hemolytic anemia is made.[14] IVIG might increase IgG catabolism, resulting in a shorter half-life of antibodies (including anti-Rh antibodies). A third hypothesis is the presence of antiidiotypic antibodies in IVIG neutralizing anti-Rh antibodies.[16, 24-26]

The use of IVIG to avoid exchange transfusion in HDN was reported in many studies with different methodology in terms of dose and frequency of administration of IVIG, type of hemolytic disease and other inclusion criteria and hence the results were conflicting and variable. A single dose of 0.5 gm/kg reduced the need for exchange transfusion without producing immediate adverse effects in term neonates with ABO[12] or Rh hemolytic disease.[27] Low-dose IVIG (0.5gm/kg) was as effective as high dose (1gm/kg) in reducing the duration of phototherapy and hospital stay, but less effective in avoiding exchange transfusion in Rh hemolytic disease of newborn.[23] Tanyer et al,[28] looked at single versus multiple dose IVIG, and found that multiple dose IVIG resulted in a greater percentage reduction in the need for exchange transfusion in ABO and Rh HDN. Meanwhile, IVIG therapy (1gm/kg), single or multiple doses, did not obviate the need for exchange transfusion and erythrocyte transfusion nor shorten hospitalization time when used in combination with light emitting diode phototherapy in the treatment

of ABO hemolytic jaundice in neonates.[29] Nonspecific human immunoglobulin as single dose of 0.5gm/kg was not effective in preventing the need for exchange transfusion in neonates with rhesus hemolytic disease.[30] Prophylactic IVIG (0.75 gm/kg) did not reduce the need for exchange transfusion nor the rates of other adverse neonatal outcomes.[31]

Our study showed significant decrease in mean duration of intensive phototherapy which is consistent with other studies[12,16,32] This difference might reflect the continuing effect of IVIG in controlling the hemolytic process and hence the need for longer use of phototherapy. Minimizing phototherapy exposure will decrease its associated hazards such as retinopathy, skin rash and frequent loose green bowel motions and bronze baby syndrome.[23] In another study, IVIG in a dose of 0.5gm/kg for 2 days administered to 8 Rh isoimmunized babies was effective in reducing the need for exchange transfusion but duration of phototherapy was comparable in IVIG and non IVIG groups.[21]

We noticed significant reduction in the length of hospital stay when IVIG was administered. Mean hospital stay was measured solely for the duration needed to treat the hemolytic disease, as neonates, who developed clinical sepsis, needing to extend their length of stay to complete the antibiotic course, were excluded from the study. This was the main reason why the length of stay in our babies who received IVIG was significantly shorter in comparison with other studies which reported significant reduction in the length of hospital stay when IVIG was administered.[16, 32] This signifies the value of IVIG in decreasing the hospital stay hazards, thereby ameliorating nosocomial infections and decreasing time where the infant is separated from his mother to promote and support successful breastfeeding.[23]

Our neonates tolerated well the high dose of IVIG without apparent drug-related adverse events as reported by others.[12,16,32] Necrotizing entero-colitis in newborns with hemolytic disease was reported as a complication of treatment with IVIG.[13,33] Transfusions for late anemia were reported to be increased in babies who received IVIG in some studies.[14-16] This was explained by the fact that antibody-sensitized neonatal erythrocytes bind to the Fc sites on the surface of the reticuloendothelial cells which have become free after the effect of IVIG had faded, causing late hemolysis. In our patients, severe late anemia requiring up blood transfusion was not encountered.

CONCLUSION

We conclude that a single high dose of IVIG could be a safe and effective therapy for reducing the need for exchange transfusion and duration of phototherapy and hospital stay in significant hyperbilirubinemia of Rh and ABO hemolytic disease of neonates. The financial saving from shortened inpatient stay and duration of phototherapy offsets the cost of IVIG.

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