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ORIGINAL PAPER

Early intravenous immunoglobin (two-dose regimen) in the management of severe Rh hemolytic disease of newborn—a prospective randomized controlled trial

Mohsen Saleh Elalfy · Nancy Samir Elbarbary · Heba Wegdan Abaza

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Abstract Phototherapy is the standard treatment in moderately severe hemolytic disease of newborn (HDN), whereas exchange transfusion (ET) is the second line in progressive cases. Intravenous immunoglobin (IVIG) has been suggested to decrease the need for ET. We aimed at assessing the efficacy of early two-dose regimens of IVIG to avoid unnecessary ET in severe Rh HDN. The study included 90 full-term neonates with Rh incompatibility unmodified by antenatal treatment and not eligible for early ET and which were randomly assigned into one of three groups: group (I), treated by conventional method; groups IIa and IIb received IVIG once at 12 h postnatal age if PT was indicated, in a dose of 0.5 and 1 g/kg, respectively. Analysis revealed 11 neonates (22%) in the conventional group and 2 (5%) in the intervention group who administered low-dose IVIG at 12 h, while none in group IIb required exchange transfusion ($p=0.03$). Mean bilirubin levels were significantly lower during the first 96 h in the intervention group compared to the conventional group ($p<0.0001$). Shorter duration of phototherapy (52.8±12.39 h) and hospital stay (3.25±0.71 days) in the IVIG group compared to conventional group (84±12.12 h and 4.72 ±0.78 days, $p<0.0001$, respectively) were observed. We conclude that IVIG administration at 12 h was effective in the treatment of severe Rh HDN; the low-dose IVIG (0.5 g/kg) was as effective as high dose (1 g/kg) in reducing the duration of phototherapy and hospital stay, but less effective in avoiding exchange transfusion.

Keywords Rh hemolytic disease of newborn · Intravenous immunoglobulin · Exchange blood transfusion · Phototherapy

M. S. Elalfy (✉)
Department of Pediatric Hematology, Faculty of Medicine,
Ain Shams University Cairo,
2 Sayed Zakaria Khalil, No 2 Elalfy,
Morbah 1153, Egypt
e-mail: elalfym@hotmail.com

N. S. Elbarbary
Department of Pediatric Hematology, Faculty of Medicine,
Ain Shams University Cairo,
25 Ahmed Fuad St. Saint Fatima,
Heliopolis, Cairo 11361, Egypt
e-mail: nancy_elbarbary@yahoo.com

H. W. Abaza
Neonatal ICU, El Galaa Hospital,
Cairo, Egypt
e-mail: abaza4u@hotmail.com

Introduction

Neonatal jaundice is one of the commonly seen neonatal problems as it affects 60% of full-term infants and 80% of preterm infants in the first few days of birth. Although transient, the condition accounts for up to 75% of neonatal care unit readmission in the first week after birth [4].

One of the main causes of severe hemolytic disease of the newborn (HDN) is Rh incompatibility, with a risk of acute or chronic kernicterus [16]. Many Rh-negative mothers in developing countries do not receive Rh prophylaxis when they give birth to Rh-positive baby due to inadequate care or inability to afford anti-D immunoglobulin [6].

Phototherapy, which is the standard modality used in moderately severe neonatal hyperbilirubinemia, may be not enough, and exchange transfusion (ET) in the proper time could avoid the risks of encephalopathy, though exchange transfusion is a therapy which is not devoid of risk [22, 24]. Moreover, the criteria used to determine the need for exchange transfusion are controversial. Severe anemia and presence of a rapidly increasing bilirubin level despite

optimal phototherapy in the first 12 h of life indicate the need for earlier intervention [13]. This makes gauging the appropriate time to intervene with exchange transfusion a difficult clinical decision [28].

In recent years, intravenous immunoglobulins (IVIG) have been successfully used in isoimmune hemolytic anemia (Rh incompatibility) [20, 26]. However, consensus guidelines on the optimum timing, exact dosage, and frequency of IVIG treatment in these circumstances are still lacking. In this prospective trial, we studied the effect of the early administration of IVIG at 12 h in a two-dose regimen for term neonates with severe Rh incompatibility, on serum bilirubin levels, need for exchange transfusion, duration of both phototherapy, and hospitalization.

Materials and methods

This prospective randomized control study was conducted on 90 neonates with Rh isoimmune hemolytic jaundice admitted in the neonatal care unit in El Galaa Hospital not eligible for ET during the first 12 h of postnatal life. The neonates were randomly assigned into one of two groups: conventional group (n=45), to be treated by PT alone and served as a comparative group; intervention group (n=45), subdivided into IIa (23 neonates) and group IIb (22 neonates) to be treated by two different doses of IVIG at 12 h postnatal age in addition to PT. The study was approved by the Ethical Committee of Ain Shams University Hospital. Informed consent from the parents was obtained before randomization, and the physician who carried out the randomization was different from that conducting the study. Conventional and intervention groups included newborns with Rh HDN who fulfilled the following inclusion criteria: (1) term neonates more than 38 weeks' gestational age born to Rh-negative mothers who never received anti-D after previous deliveries; (2) isoimmune hemolytic jaundice proven by Rh incompatibility between blood group of the mother and the baby, positive direct Coombs' test, and high reticulocytic count; and (3) significant indirect hyperbilirubinemia requiring phototherapy in the first 12 h of life and/or rising by (0.5 $mg\,dL^{-1}h^{-1}$) while serum bilirubin level is still below the exchange transfusion criteria on admission according to American Academy of Pediatrics (AAP) management guidelines for hyperbilirubinemia [2].

Neonates were excluded if they had any of the following: (1) preterm and near-term neonate <37 weeks' gestational age, (2) perinatal asphyxia, (3) neonatal sepsis, and (4) neonates with hematomas. Maternal and delivery histories were reviewed thoroughly for all subjects; none of patients had a history of prenatal treatment (maternal IVIG) and/or in utero transfusion.

The intervention and conventional groups were subjected to the following:

Clinical examination

This includes assessment of APGAR score at 1 and 5 min to exclude perinatal asphyxia. Gestational age was assessed by new Ballard score, general examination excluding the presence of trauma, e.g., cephalohematoma and local examination, including: (1) neurological examination to detect the state of consciousness, signs, and stage of bilirubin encephalopathy and (2) abdominal examination to detect any organomegaly.0

Total serum bilirubin

For all neonates, blood samples (0.5 mL each) were obtained for the measurement of total bilirubin levels shortly after birth (mean 1.8±0.4) and was repeated every 6 h in all neonates unless indicated more frequent until cessation of phototherapy and 24 h later. The total bilirubin level is measured automatically using a spectrophotometer (RA 50). Other investigations were carried out: basal complete blood count, reticulocytic count, Coombs' test, and C-reactive protein.

Phototherapy

The baby is placed naked with a fiber-optic blanket on his undersurface, covering the eyes and genitalia, at a distance of 30–40 cm from special blue light source; four lamps were used in an incubator and body position was changed continuously. Initiation and discontinuation of phototherapy was according to the serum bilirubin levels as provided by the AAP guidelines [2]. The total duration of phototherapy as well as the total duration of hospital stay were calculated and recorded.

Intravenous immunoglobulin

Baseline and follow-up bilirubin blood samples had been obtained and the diagnosis was established. At 12 h after birth, neonates in the intervention group received a single dose of intravenous immunoglobulin (CSL Behring) using an infusion pump over 3 h of 0.5 g/kg (for group IIa) and over 6 h of 1 g/kg (for group IIb). Neonates were monitored closely for side effects that might be related to the administration of IVIG. Vital data were monitored and recorded for all neonates.

Exchange transfusion

When bilirubin level increased by 1 $mg\,dL^{-1}h^{-1}$, the neonate will require exchange transfusion according to the guidelines of the AAP [2]. The exchange transfusion is done in cycles: Each one usually lasts a few minutes. The baby's blood is slowly withdrawn (about 20 mL at a time, depending on the patient's size and the severity of illness). An equal amount of fresh, pre-warmed blood or plasma flows into the patient's body. This cycle is repeated until the correct volume of blood has been

replaced. After the exchange transfusion, catheters may be left in place in case the procedure needs to be repeated and removed once the procedure has ended.

Statistical analysis

All statistical analysis was performed using the SPSS, 10th version of Windows (Statistical Package for the Social Sciences). Differences for continuous variables were examined using ANOVA test (data were presented as mean and SD), whereas for categorical variables, differences were assessed using the χ^2 test (results were presented as percentages and the corresponding p value). To control for multiple comparisons, a Bonferroni adjustment was used to declare statistical significance at 0.05 levels. Non-parametric data were tested using Kruskal–Wallis test pairwise comparison using Mann–Whitney test with Bonferroni correction; critical level of significance will be ≤0.016.

Results

A total of 90 neonates were enrolled in the study and stratified into conventional and intervention groups over a period of 10 months from March 2009 to January 2010. However, five parents of the intervention group did not consent using IVIG, so they were treated eventually by the conventional method (n = 45 + 5 = 50). Of the 40 infants finally in the intervention group, five babies assigned to the high IVIG dose (n = 20 − 5 = 15); their parents chose the lower dose (n = 20 + 5 = 25).

All neonates (47 males and 43 females) had stable general condition with unremarkable systemic examination. Their median gestational age was 38.5 weeks and their median birth weight was 3,100 g. The two groups were similar at baseline in demographic, clinical, and biochemical characteristics (Table 1). All of the pretreatment parameters were well balanced between the conventional and intervention groups of patients. There were no significant differences between groups regarding their mean gestational age (p=0.5), gender (p=0.99), maternal diabetes (p=0.37), mode of delivery (p=0.98), and mean birth weight (p=0.94). Also, the same findings were noticed regarding laboratory parameters as Hgb (p=0.97) and reticulocytic count (p=0.08), which were statistically non-significant among the two studied groups.

Changes in bilirubin level

The initial bilirubin level at a mean 1.8±0.4 h and at 12 h did not differ between the two groups, with a mean of 10.86±0.63 and 13.49±0.88 mg/dL for the conventional group and 10.94±0.81 and 14.24±1.44 mg/dL for the intervention group (p=0.23, p=0.18), respectively. During the follow-up of serum bilirubin level, the intervention group had significantly lower mean levels than the conventional group (Fig. 1). At 24 h, mean serum bilirubin level was 15.4±1.72 mg/dL for the conventional group compared to 13.79±1.15 for the intervention groups (p< 0.001). At 48 h, mean serum bilirubin level was 13.72± 1.71 mg/dL for the conventional group compared to 12.37± 1.82 for the intervention groups (p<0.01). At 72 h, mean serum bilirubin level was 12.90±1.37 mg/dL for the conventional group compared to 11.84±1.17 mg/dL for the intervention groups (p=0.4), while at 96 h, mean serum bilirubin level was12.15±0.49 mg/dL for the conventional group compared to 10.56 ± 0.67 mg/dL (p=0.03) for the

Table 1 Comparison between the three studied groups according to demographic, clinical, and biochemical characteristics of neonates with Rh HDN (n=90)

	Conventional (n=50)	Intervention (n=40)		p value
		IIa (n=25)	IIb (n=15)	
Birth weight (g), mean±SD[a]	3,064.00±383.20	3,100.00±387.30	3,073.33±490.58	0.94
Gestational age (weeks), mean±SD [a]	38.70±0.86	38.48±0.71	38.53±0.74	0.5
Male, n (%)[b]	26 (52%)	13 (52%)	8 (53%)	0.99
Delivery mode, n (%)[b], cesarean section	32 (64%)	16 (64%)	10 (66%)	0.98
History of maternal diabetes(+ve)[b]	4 (8%)	3 (12%)	2 (13%)	0.37
Hgb (g/dL, median, IQ range)[c]	12.5 (11.00–13.40)	12.5 (12.00–13.90)	12.5 (11.5–13.15)	0.97
Reticulocytic count (%, IQ range)[c]	9.15 (5.50–12.00)	8.3 (5.90–11.750)	11.6 (9.5–12.9)	0.08

IQ interquartile range

[a] Anova test was used

[b] The chi-square test was used

[c] Krukal–Wallis test (using Mann–Whitney test with Bonferroni corrections)

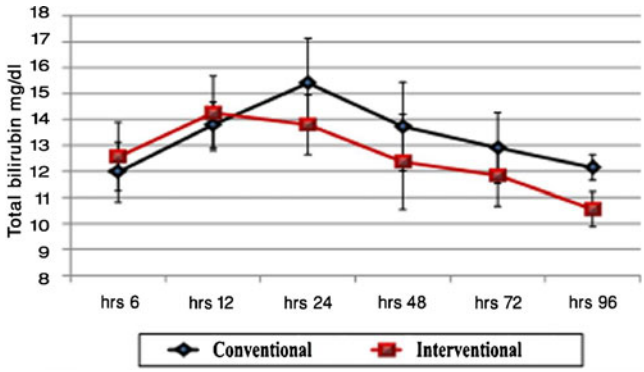

Fig. 1 Comparison between the two studies groups regarding bilirubin level initially and subsequent post-neonatal hours of life. Mean serum bilirubin level was significantly lower comparing the intervention groups with the conventional group, especially at 24, 48, and 96 h ($p<0.0001$, $p<0.0001$, $p=0.03$, respectively)

intervention groups, which indicates that IVIG ameliorates the rise of bilirubin level when it is administrated.

The percentage of change in serum bilirubin demonstrated that the conventional group showed an increase of its level at 24 and 48 h (19.05±8.42% and 7.96±10.25%, respectively), while a drop in bilirubin level was observed in group IIa (9.26±8.08% and 21.90±8.15%) and group IIb (12.63±7.24% and 26.81±7.31%, respectively). This rate of drop was significant comparing both the intervention groups with the conventional group ($p<0.0001$), but no difference was noted between the two intervention groups ($p=0.24$ after24 h and $p=0.11$ after 48 h).

Duration of phototherapy

The duration of phototherapy in terms of hours was significantly shorter in the intervention groups (52.80± 12.39 h) than in the conventional group (84±12.12 h, $p<0.0001$).Duration of phototherapy was comparable between the two intervention groups (54.72±14.73 vs. 49.60±6.20 h, $p=0.2$). At 72 h, 80% ($n=20$) of neonates in group IIa and 93.4% ($n=14$) of neonates of group IIb were off phototherapy, while all neonates at the conventional group were still in need of phototherapy. At 96 h, 92% ($n=23$) of neonates in group IIa and 100% ($n=15$) of neonates of group IIb were off phototherapy, while 50% ($n=25$) of neonates at the conventional group were still in need of phototherapy.

Duration of hospital stay

Duration of hospital stay was significantly shorter in the intervention groups, with a mean of 3.25±0.71 days when compared to the control group, with a mean of 4.72±0.78 days ($p<0.001$), with no difference between the two intervention groups 3.36±0.86 vs. 3.07±0.26 h ($p=0.32$).

Exchange transfusions

After the treatment had commenced, 11 patients (22%) in the conventional group required exchange transfusions, whereas two (5%) exchange transfusions were performed in the intervention group, two neonates in group IIa, and none in group IIb ($p=0.03$). There was no statistically significant difference comparing the two intervention groups ($p=0.52$). The two neonates in group IIa requiring exchange transfusion were at 30 and 33 h, respectively (Fig. 2). No cases required multiple exchange transfusions and no deaths were related to this procedure in either treatment group.

Neonates tolerated well the IVIG without apparent drug-related adverse events, including fever, meningismus, allergic reactions, and volume overload.

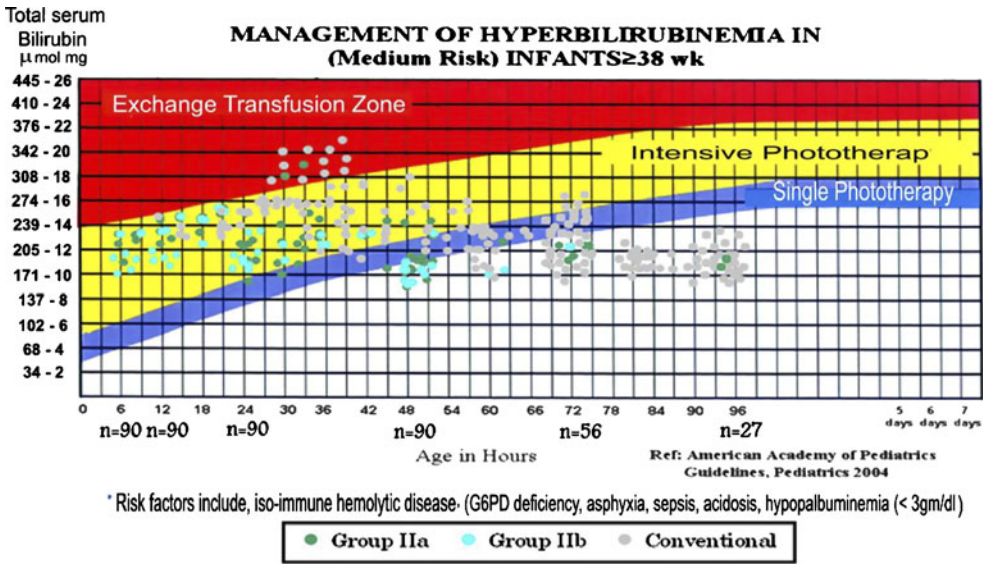

Fig. 2 Follow-up of mean serum bilirubin levels in conventional and intervention groups throughout the course of treatment. Early administration of IVIG at 12 h in the intervention group has led to a marked decrease of the need of exchange transfusion (5%) in the intervention group (two neonates in group IIa and none in group IIb), contrasting 11 patients (22%) in the conventional group ($p=0.03$). *The total numbers of patients at 6, 12, 24, and 48 h were 90 neonates and 56 neonates at 72 h and 27 neonates at 96 h

Discussion

Rh hemolytic disease of the newborn, once a major cause of perinatal mortality and long-term disability, is rarely seen in developed countries today [25]. Bilirubin levels can rise quickly in the first hours of postnatal life, and interventions must be prompt to prevent side effects related to hyperbilirubinemia [29]. The reduction in the frequency of disease occurrence has followed the understanding of its pathophysiology, the development of reliable diagnostic tools, the widespread use of Rh-immune globulin prophylaxis [19, 21], and, for those cases slipping through the prevention system, the availability of treatment by intrauterine blood transfusions, which together constitute one of the great advances in modern medicine [10, 17, 27].

However, hemolytic disease of the newborn has unfortunately continued to contribute to perinatal and neonatal morbidity and mortality in developing countries that do not have access to this health care technology [6]. In El Galaa Maternity Hospital, Ministry of Health (study venue) with about annual 30,000 deliveries and 1,500 neonatal admissions, the annual exchange transfusions had dropped to one tenth in two decades following the implementation of Rh-immune globulin prophylaxis, although not effective completely (personal communication).

The use of IVIG has declined the number of infants needing exchange transfusion, as suggested by many studies [23, 26, 30]. The benefits of IVIG therapy appear to be related to the blockage of Fc receptors in the neonatal reticuloendothelial system [11]. This subsequently stops the destruction of RBCs, thus competing with anti-D sensitized neonatal erythrocytes and preventing further hemolysis [5, 23]. The higher dose IVIG avoided ET; this could be attributed to its ability to block more Fc receptors which might prevent further elevation of bilirubin to exchange level.

The duration of phototherapy in terms of hours was significantly shorter in the intervention groups (52.80± 12.39 h) than in the conventional group (84±12.12 h, $p<$ 0.0001),while comparable results were found between both intervention groups. Hence, IVIG administration reduced the duration of phototherapy at least by 30 h. The effect of IVIG, despite the variation in doses, seems to have a beneficial effect of controlling the severity of hemolytic process. Decreasing hours of phototherapy the neonates were subjected to will decrease hazards of phototherapy, such as retinopathy, skin rash, and frequent loose green bowel motions and bronze baby syndrome. The change in infant's thermal environment may lead to an increase in peripheral blood flow and insensible water loss [18]. This finding is consistent with previous studies that reported shortened phototherapy duration in IVIG group [1, 20, 31]. In contrast, other studies [23] reported that there was no statistical significant difference between IVIG and control group.

Duration of hospital stay was significantly shorter in the intervention groups compared to the conventional group ($p<$ 0.0001), with no difference between the two intervention groups (p=0.32).This signifies the importance of IVIG in decreasing the hospital stay hazards, hence decreasing nosocomial infections and decreasing time where the neonate is separated from his mother to promote and support successful breastfeeding. This is supported by a recent systematic review of randomized controlled trials of IVIG administered in the postnatal period in HDN [12], showing a significant effect for IVIG in reducing the length of hospital stay, whereas other studies [17] did not prove the effect of IVIG regarding hospital stay period.

Severe Rh HDN is a common disease with a serious form of consequence and does need invasive intervention if not responding to phototherapy, especially in the first hours of life where bilirubin toxicity to the brain is very harmful and common in that critical timing.

Our study is the first to report the impact of early IVIG administration on the need of exchange transfusion in neonates with severe HDN. It is worth noting that timely decision regarding early IVIG administration at 12 h of life for the management of neonates with Rh HDN has radically improved the outcome of these neonates and decreased the need of exchange transfusion. Most probably, the two cases in the low-dose group who needed ET were severe to the degree that it could be hypothesized that low-dose IVIG could not block the ongoing hemolysis to ameliorate the condition, and this made the need of exchange transfusion inevitable. However, designing a curve to set the proper timing of IVIG administration according to bilirubin levels is recommended.

A single dose of 0.5 g/kg IVIG at 12 h was not as effective as the higher dose. If the smaller dose of IVIG therapy should be considered, it could be used earlier than 12 h or be repeated if necessary. The effect of IVIG to decline the need of ET was consistent with the results of previous studies [1, 15, 23, 28, 31]. IVIG administered directly after the diagnosis of neonatal jaundice increased the chance of omitting ET and reduced the duration of phototherapy; it also protected against morbidity-induced hyperbilirubinemia. Some authors have implied that the key to a successful treatment is the early administration of the immunoglobulin, as soon as the diagnosis of hemolytic anemia. Neonates tolerated well the high dose of IVIG without apparent drug-related adverse events, in contrast to others where necrotizing enterocolitis in newborns with hemolytic disease has been detected [8, 26].

A previous study [1] reported that the percentage of neonates in need for exchange transfusion after IVIG

therapy was 12–14%; this is lower than the percentage reported previously by another study [9] who found that 21% of neonates in low- and high-dose groups needed exchange blood transfusion after IVIG therapy. This may be due to more severe cases being enrolled in their study.

The morbidity and mortality associated with exchange blood transfusion are not insignificant [3, 7]. Moreover, the mortality rate of exchange transfusion, which is the oldest treatment modality for hyperbilirubinemia, has been reported to be between 0.3% and 1.2% [14]. However, the morbidity rate associated with exchange transfusion is about 5% [2]. Thus, we determined that rhesus sensitization in its severe form in neonates, who, according to former standards, would have been candidates for invasive and risky procedure as exchange transfusion, can be managed expectantly by the early administration of IVIG in the first 12 h of life. The financial saving from the shortened inpatient stay and duration of phototherapy may offset the cost of IVIG.

Our study revealed no statistical difference regarding maternal history of diseases (gestational diabetes), and this was in agreement with a previous study [32] who found no significant difference between the studied groups in the severity of maternal diseases.

Our study has certain strengths and limitations: This is the only randomized controlled trial comparing two different dose regimens of IVIG (0.5 vs. 1.0 g/kg of IVIG) with phototherapy alone and timing of administration in neonates with Rh incompatibility. Previous studies on the use of multi-dose IVIG [31] suggest that multiple doses of IVIG block ongoing hemolysis, thus decreasing the need for blood transfusion for late anemia, whereas a single dose may stop the process only temporarily. They propose that the use of multi-dose IVIG therapy could significantly reduce the rate of exchange transfusions, the adverse effects associated with them, and the length of hospitalization in infants with hemolytic anemia. However, the optimum treatment dose and frequency is as yet uncertain, and this may be an area for study.

Conclusion

It may well be justified to electively use IVIG at 12 h in high-risk phototherapy group of patients with HDN where the likelihood of exchange transfusion is great—that is, neonates with Rh disease unmodified by antenatal treatment and the neonates has suffered from severe disease which may require exchange transfusion. IVIG at 12 h of life to neonates with immune hemolytic hyperbilirubinemia was effective in decreasing the need of exchange transfusion, shortening the duration of phototherapy and hospital stay when combined with conventional phototherapy. Designing a curve to set the timing of IVIG administration according to both clinical settings as well as bilirubin level in order to reduce the need for an invasive procedure as exchange transfusion is warranted.

Conflict of interests The authors declare that they have no conflict of interests.

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