Original Article

Intravenous Immunoglobulin in Hemolytic Disease of the Newborn: A Moving Target in Time

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Abstract

Background: Alloimmune hemolytic disease of the newborn (AIHDN) results in hemolysis, anemia, hyperbilirubinemia with the potential for brain damage. Intravenous immunoglobulin (IVIG) has been investigated as an alternative low-risk procedure for the treatment of AIHDN in addition to traditional treatment methods such as phototherapy and exchange transfusion (ET). **Aim:** To evaluate the effectiveness of IVIG therapy in decreasing ET needs based on risk factors and clinical outcomes. **Materials and Methods:** Charts of neonates born >30 weeks of gestation who underwent phototherapy and were administered IVIG therapy due to AIHDN between January 2013 and July 2018 were retrospectively reviewed. **Results:** Sixty-three neonates were included in our study. Forty-three of them (68.3) % were full-term infants. ABO incompatibility (n = 33, 52.4%) was the major cause of AIHDN (n = 63). Additional risk factors for jaundice were found to coexist in 95.2% (n = 60) of the infants. Fifteen infants (23.8%) required ET, mostly due to Rh incompatibility (n = 11, 73.3%). Mortality was observed in 3.2% (n = 2) of the patients, 1.6% (n = 1) of whom were related to ET. Serum albumin value was found to be negatively correlated with the requirement for ET (r = 0.713, $P < 0.001$), whereas serum bilirubin albumin ratio was positively correlated (r = 0.489, _$P < 0.001$). Nine (14.3%) infants needed a simple transfusion during the hospitalization period, whereas five (7.9%) infants had readmission for simple transfusion after discharge. Apnea was the only complication seen in one (1.6%) patient. **Conclusion:** IVIG treatment should be considered due to its relative benefits when compared to exchange transfusion. In addition to its safety, it is a less complicated treatment modality with low side effect rates. It may be justified for elective use in neonates suffering from AIHDN, who will require ET with a risk of mortality by decreasing the peak of total serum bilirubin levels.

Keywords: *Alloimmune hemolytic disease of the newborn, exchange transfusion, intravenous immunoglobulin, phototherapy*

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Introduction

Hemolytic disease of the fetus and newborn (HDFN) is observed when the breakdown of both fetal and neonatal red blood cells (RBC) occurs due to placental crossing of maternal IgG class antibodies. These antibodies may be natural or derived from previous sensitization. Intravenous immunoglobulin (IVIG) acts by blocking Fc receptors on macrophages, which reduces the breakdown of antibody-coated RBCs and lowers the serum bilirubin level. The recommended dose of IVIG is 0.5–1 g/kg.[1-3] Exchange transfusion (ET), as well as phototherapy (PT), are conventional treatment modalities for isoimmunization. It has been suggested

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that IVIG could be used in HDFN to lower the requirement for ET. As a treatment modality, ET has infectious, thrombotic, and metabolic complications. To avoid the associated neurological complications because of risks of ET, IVIG could be suggested as a beneficial treatment modality[3,4] Due to the recommendations by the American Academy of Pediatrics (AAP), the use of IVIG increased steadily until 2018 when a Cochrane review found that insufficient evidence existed to prove that IVIG prevented ET in neonates with HDFN.[5] To date, due to the conflicting outcomes in the literature, this study aimed to evaluate the potential effect of IVIG on decreasing ET rates in infants with HDFN with predisposing factors like breastfeeding and B/A ratio. Neonatal hyperbilirubinemia occurs more frequently in breastfed infants.[6] Various factors like poor caloric intake, dehydration, and increased enterohepatic circulation have been implicated for the early-onset breastfeeding jaundice.[7] The B/A ratio has been shown to correlate with unbound bilirubin and can be used in the decision to initiate PT or ET.[4,8]

Clinical presentation of HDFN may vary from anemia to hydrops and hyperbilirubinemia to kernicterus in Rhesus-mediated hemolytic disease.[9] RhD prophylaxis, Doppler ultrasonography, intrauterine blood transfusions (IUTs), noninvasive fetal RhD typing with cell-free DNA from maternal plasma, and similar advances in the care of neonates have resulted in a significant decrease in perinatal morbidity and mortality. This decrease in incidence means that hemolysis is observed in only around 15% of pregnancies in which ABO incompatibility is present.[10] Although anti-A and anti-B antibodies are mostly of IgM class, pregnancy may lead to an increase of these antibodies from the IgG class. The incidence of HDFN secondary to ABO incompatibility differs between populations with its incidence reported to be 17% in Black, 15% in Asian, 14% in Caucasian, and 12% in Hispanics.[11]

Materials and Methods

This retrospective cohort study recruited patients for inclusion between January 2013 and July 2018. The study was conducted at a tertiary referral center with 65 incubators and over 2000 newborn admissions per year), following local ethic board approval (Approval Date: 03.07.2018 Approval No: 31.

Medical data of neonates hospitalized in the NICU were evaluated, and neonates of >30 weeks gestational age that underwent PT secondary to high serum bilirubin levels as stated by AAP were recruited. The criteria stated by AAP included total serum bilirubin level that changes with postnatal age and risk factors (e.g isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, sepsis, temperature instability, acidosis, or albumin <3.0 g/dL).[4]

Those with the following were excluded: (1) Neonates with hematomas, (2) Neonatal sepsis, and (3) Perinatal asphyxia.

All patients were subjected to the following investigations and interventions:

1. Cord blood sampling was taken for direct antiglobulin test (DAT) for isoimmunization.
2. After initiation of phototherapy, serum total bilirubin levels were measured every 4 h until the rate of increase was determined.
3. In babies with HDFN, according to our unit protocol, IVIG was administered either when the bilirubin level reached the phototherapy threshold in the presence of significant hemolysis or if the bilirubin value was 2 mg/dL below the exchange level.
4. The presence of significant hemolysis was determined according to the increase in bilirubin and decrease in hemoglobin levels.
5. Phototherapy and exchange curves are used to determine the need for PT and ET, defined by AAP.[4]
6. Neonates received a single 1.0 g/kg dose of IVIG over a 2 h period and were thereafter observed for possible adverse effects of IVIG therapy like anaphylaxis, pulmonary embolism, renal failure, thrombosis, necrotizing enterocolitis, fever, apnea, vomiting, skin rash, cyanosis, hypotension, hypothermia, irritability, the transmission of blood-borne diseases, transfusion-related acute lung injury, aseptic meningitis syndrome and severe hemolysis. As all babies were monitored for vital signs (e.g. temperature, blood pressure, respiratory status, heart rate, urine and stool output) and physical examinations were performed in NICU, an unexplained change in these findings was evaluated for adverse reactions of IVIG therapy.
7. When the bilirubin levels were 2–3 mg/dL below the PT level (stated by AAP phototherapy graphs), PT was discontinued.[4]
8. The infants were closely observed for the development of rebound hyperbilirubinemia for 24–48 h by venous bilirubin measurement thereafter, defined as bilirubin level reaching the PT threshold.
9. ET was indicated, as suggested by AAP when bilirubin levels rose by 1 mg/dL/h.[2]

Anemia requiring simple transfusion was defined according to the postnatal age and ventilation support of preterm infants as stated in the Cochrane Database of Systematic Review (Hb levels 11.5 g/L 1st week, 10 g/L 2nd week, 8.5 g/L 3rd week with respiratory support versus

Hb levels 10 g/L 1st week, 8.5 g/L 2nd week, 7.5 g/L 3rd week without respiratory support).[12] Gestational age of neonates upon delivery was classified as early preterm (<34 weeks), late preterm (34–36 6/7 weeks), term (37–40 6/7), and post-term (>42 weeks).[13] Jaundice was the yellowish discoloration of the infant's skin and sclera when total serum bilirubin levels rise. Neonatal hyperbilirubinemia was defined as total serum bilirubin levels greater than the 95th percentile for age within the first six days of life.[6]

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows (IBM Corp. Released 2017, Version 25.0. Armonk, NY, USA) and presented as numbers and frequencies. Continuous variables were expressed as mean ± standard deviation (SD) or median [Interquartile range (IQR)]. In continuous variables, data normality was tested using the Kolmogorov–Smirnov test. Categorical data were expressed as n (%). Nonparametric data were tested using the Wilcoxon –t-test, and parametric data were tested using the Paired-Samples t-test. The Spearman test was used for correlation analysis. Statistical significance was established when $P < 0.05$.

Results

Of the 6,600 patients, the records of 960 neonates born >30 weeks of gestation who underwent phototherapy were reviewed for eligibility. Of these, 85 infants were found to have used IVIG in addition to phototherapy due to HDN. Exclusion criteria were neonates with hematomas (n = 7), neonatal sepsis (n = 10), perinatal asphyxia (n = 5). Following the exclusion of these patients, 63 infants (40 females and 23 males) with a median gestational age of 38 weeks and average birth weight of 3055 ± 611 g were included in the study. Figure 1 shows the CONSORT diagram for the study.

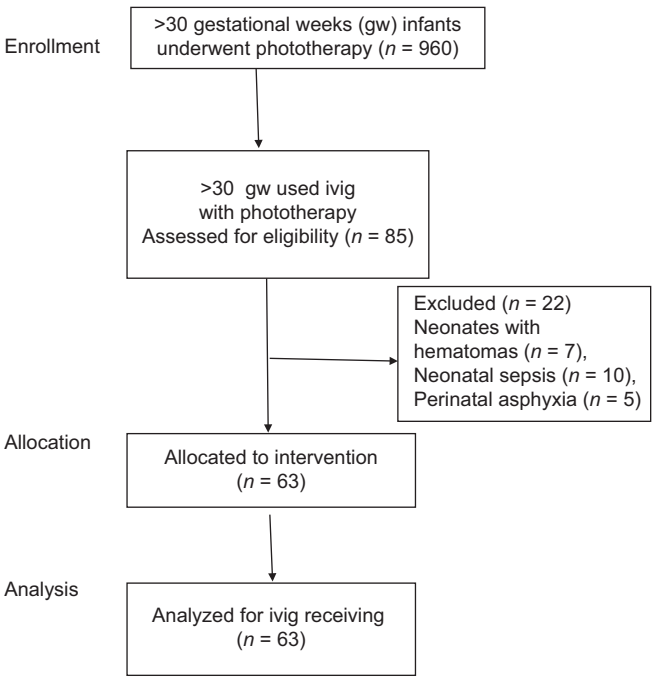

Figure 1: CONSORT chart for selection of eligible infants in the study

The majority of 63 infants participating in the study were full-term (68.3%, n = 43), and HDFN was most commonly observed due to ABO incompatibility (52.4%, n = 33). Preterm infants (30.1%, n = 19) involved in the study were <34 weeks (7.9%, n = 5) and 34–37 weeks (late preterms) (22.2%, n = 14) [Table 1]. Intrauterine transfusion was done in four (6.3%) of the patients. Sixty (n = 95.2%) of the neonates had an additional risk factor for jaundice present. The most commonly observed among these factors were

Table 1: Demographic and Clinical Characteristics of Neonates with HDFN* Treated by Phototherapy and IVIG**

Characteristics	*n* (%)
Gestational age (weeks), median, IQ range	38 (36-40)
Early preterm (<34 weeks)	5 (7.9)
Late preterm	14 (22.2)
Full-term	43 (68.3)
Post-term	1 (1.6)
Birth weight (g), mean±SD	3055±611
Male gender	23 (36.5)
Caesarean section	22 (34.9)
Incompatibility	
Rhesus	24 (38.1)
Major blood group (ABO)	33 (52.4)
Minör blood group	1 (1.6)
Rhesus and minor blood group	3 (4.8)
Others	2 (3.2)
Presence of intrauterine transfusion	4 (6.3)
Presence of additional risk factors	61 (96.8)
Prematurity	10 (15.9)
Sibling with PT¶ or ET¶¶	2 (3.2)
Breastfeeding	41 (65.1)
Prematurity and breastfeeding	8 (12.7)
First symptom	
İcterus	52 (82.5)
Anemia	7 (11.1)
Hydrops	1 (1.6)
Anemia and hydrops	3 (4.8)
Timing of the first symptom (h), median, IQ range	24 (10-24)
Positive DAT test	63 (100)

*Hemolytic disease of the fetus and newborn, **Intravenous immunoglobulin. ¶Phototherapy, ¶¶Exchange transfusion

Table 2: Clinical Outcomes of Neonates with HDFN* Treated by Phototherapy and IVIG**

Outcome	*n* (%)
Hb§ at birth (g/dL, median, IQ range)	14.7 (13.2-17.1)
Hb at discharge (g/dL)	12.6±2.5
TSB value at ivig therapy (mg/dL)	12.6±4.5
Peak TSB value (mg/dL median, IQ range)	15.4 (13.7-17.3)
Rebound hyperbilirubineia	15 (23.8%)
TSB¶ value at discharge	9.3±3.4
Albumine value at ivig therapy (g/dL median, IQ range)	3.4 (2.9-3.6)
Need for exchange transfusion	15 (23.8%)
Rhesus	11 (73.3%)
Major blood group (ABO)	1 (6.6%)
Minör blood group	1 (6.6%)
Rhesus and minor blood group	1 (6.6%)
Others	1 (6.6%)
Need of RBC*** transfusion during hospitalization	9 (14.3%)
Readmission for transfusion	5 (7.9%)
İVİG complications	1 (1.6%)
Mortality	2 (3.2%)
Pretem complications	1 (1.6%)
Exchange transfusion	1 (1.6%)

*Hemolytic disease of the fetus and newborn, **Intravenous immunoglobulin, §Hemoglobin, ¶Total serum bilirubin, ***Red blood cell

breastfeeding (65.1%, n = 41), prematurity (15.9%, n = 10), prematurity and breastfeeding (12.7%, n = 8), and having a PT or exchange transfusion history in a sibling (3.2%, n = 2). The main risk factors evaluated in our study for neonatal jaundice were breastfeeding, prematurity, and previous sibling received PT or ET[14,15] The most commonly seen first symptom in patients with HDFN was neonatal jaundice (82.5%, n = 52), which was followed by anemia (11.1%, n = 7), hydrops (1.6%, n = 1) or both (4.8%, n = 3). The average time to the appearance of the first symptom was 24 h (10-24).

When compared to levels at birth, infants had lower hemoglobin values after PT and IVIG therapy [14.1 ± 3.8 vs. 12.6 ± 2.5, P = 0.001]. Total serum bilirubin level (TSB) was found to decrease after phototherapy and IVIG administration (12.6 ± 4.5 vs. 9.3 ± 3.4, P = 0.001). The average peak TSB value was found to be 15.4 (13.7–17.3) during PT and IVIG administration. Rebound hyperbilirubinemia was seen in 15 (23.8%) infants. Fifteen infants (23.8%) in our study required ET, with the most common cause found to be Rh incompatibility (73.3%, n = 11). Nine (14.3%) infants required a transfusion during the hospitalization period, whereas five (7.9%) infants had readmission for transfusion after discharge. Apnea was the only complication seen in one (1.6%) patient. The mortality rate was 3.2% (n = 2) and was related to preterm complications in one (1.6%) and ET in the other (1.6%) patient. A negative correlation was found between the requirement for ET and serum albumin value (r = 0.713, P < 0.001) and a positive correlation between the requirement for ET and serum bilirubin albumin ratio (r = 0.489, P < 0.001) [Table 2].

Discussion

The most commonly observed hemolytic disease of neonates is AIHDN. AIHDN generally occurs due to existing antibodies in Rh isoimmunization or blood group incompatibilities.[10] It is important to note that in our study more hemolysis and hyperbilirubinemia were observed in patients with ABO incompatibility when compared to patients with Rh incompatibility. Although the literature[16] reports that the use of IUTs has reduced perinatal mortality below 10%, the number of infants who received IUTs in our study group remained low. In a cohort study, Van Camp *et al*. reported that a delay in transferring the alloimmunized fetuses for IUTs to the perinatal centers decreases their chance of survival.[17]

Late preterm infants are managed as preterm neonates according to the 2004 AAP guidelines, as these guidelines do not include any specific suggestions for infants between 34th and 35th gestational weeks. Conspicuous hyperbilirubinemia requiring ET and bilirubin encephalopathy in late preterm infants can be prevented with the administration of IVIG. A systematic review reported that for prevention of ET through the use of IVIG, the number needed to treat is 2.7.[18] However, the authors of this review believe that despite this low number, considering the potential risks of hyperbilirubinemia at ET levels and the relatively high number of preterms that are faced with this situation, IVIG should be administered. Furthermore, preterms with Coombs positive hemolytic disease should also be treated with IVIG as kernicterus has been reported in preterm infants with peak serum albumin of 6.5 mg/dL.[19] Breastfeeding is also a predisposing factor for hyperbilirubinemia as breastfed infants are six times as likely to develop total serum bilirubin levels >15 mg/dL when compared to bottle-fed infants.[7,20] As breastfed infants have a fewer caloric intake and pass less stool by weight, the amount of bilirubin reabsorption increases whilst the excretion decreases.[21,22] However, this risk should not be managed by limiting breastfeeding, but on the contrary by encouraging it. In our study, more than seventy percent of infants whose bilirubin level reached the PT threshold, when hemolysis is significant, or the bilirubin value was 2 mg/dL below the exchange level were breastfed and treated with IVIG.

According to AAP, bilirubin and albumin ratio (B/A) is a factor affecting the decision to initiate phototherapy or ET. ET should be considered when this ratio is 8.0 for infants ≥38 wks, 7.2 for infants $35^{0/7}$–$37^{6/7}$ weeks and well, or ≥38 weeks if higher-risk or AIHD or G6PD deficiency and 6.8 for infants $35^{0/7}$–$37^{6/7}$ weeks if higher-risk or AIHD or G6PD deficiency.[18] Free bilirubin is considered to be the fraction that causes neurotoxicity as it can cross the blood-brain barrier.[23,24] In our study, we found that lower serum albumin values and higher B/A ratio can be an indicator for ET although IVIG therapy was given.

IVIG therapy should be commenced after careful evaluation and consideration of its side effects as well as the risks of ET. Use of IVIG has been linked to several potential side effects including anaphylaxis, hypersensitivity, pulmonary embolism, renal failure, thrombosis, necrotizing enterocolitis, fever, apnea, vomiting, skin rash, cyanosis, hypotension, hypothermia, irritability, the transmission of blood-borne diseases, transfusion-related acute lung injury, aseptic meningitis syndrome, and severe hemolysis.[9,25-30] Complications such as electrolyte imbalance, cardiac arrhythmias, embolism, necrotizing enterocolitis, and sepsis are reported to occur in around 24% of neonates undergoing ET.[16] Patra *et al.*[31] reported that ETs were associated with thrombocytopenia, hypocalcemia, and metabolic acidosis as adverse effects. The morbidity rate of ET is reported as 5%, and the mortality rate ranges between 0.3% and1.2%. We found that IVIG was well tolerated with a low adverse effect rate when compared to the risk of mortality as 1.6% in our study due to ET which is higher than reported in the literature.[32]

Al-lawama *et al.*[33] reported an increased rate of severe anemia and blood transfusion requirement with the use of IVIG at first hospitalization. The authors attributed these findings to inhibition of erythropoietin production secondary to an increase in pro-inflammatory cytokines caused by IVIG. On the other hand, increased severity of hemolysis in these infants could also be the reason for this finding. The authors reported no statistical significance for late anemia and readmission for transfusion. Several mechanisms have been proposed for late anemia such as inappropriately low erythropoietin production, intramedullary destruction of RBC precursors or free RBC population after the effect of IVIG had faded.[34] In contrast to these findings, the authors emphasized that IVIG therapy can be a risk for rebound hyperbilirubinemia. Our transfusion rates were closely concomitant to those reported in the literature; however, the rebound hyperbilirubinemia rate was lower in our group of patients.

The optimal dose of IVIG therapy and the effective number of infusions are still unknown. In our study, we used a high-dose IVIG (1 g/kg), and our ET rate was higher compared to two previous studies that used 0.5 g/kg[35] and 1–2 g/kg.[36] The direct antiglobulin test (DAT) can be used to determine the cause of hyperbilirubinemia in order to establish the correct use of IVIG. DAT can be used when there is clinical or laboratory evidence of jaundice or hemolysis. However, the presence of a negative result does not exclude causes of non-immune hemolysis of neonatal hyperbilirubinemia.[37,38] In our study, positive DAT was observed in all neonates at the time the first symptom appeared, and the most frequently observed clinical finding was icterus.

Our study has some limitations. Owing to the protocols of our unit mentioned previously and due to ethical considerations, we could not match a conventional group for controls. The Cochrane Database of Systematic Review emphasized that there was insufficient confidence to estimate the effect of IVIG, despite the studies that show IVIG reduces hemolysis.[5] On the other hand, systematic reviews and meta-analyses have concluded that different thresholds of bilirubin, dosages used, and brand of IVIG as well as advances in the field of PT over time may lead to the risk of bias in studies previously reported.[1]

Nevertheless, our study has demonstrated IVIG to be a less invasive and effective treatment method, having fewer adverse effects when compared to ET. Furthermore, to our knowledge, our study is the first to report albumin levels and B/A ratio are the major factors of ET requirement and can be predictors of failure of IVIG treatment.

Conclusion

Following risk-to-benefit analysis, IVIG should be used electively in the high-risk group of patients who have significant hemolysis and hyperbilirubinemia despite undergoing PT and are approaching the ET threshold. It remains unclear why some neonates respond to IVIG therapy and why others do not. Conflicting outcomes reported in the literature necessitates high-quality prospective studies adequately to shed light on the role of IVIG in AIHDN.

What is already known?

Alloimmune hemolytic disease of the newborn is being treated by traditional treatment methods such as phototherapy and exchange transfusion with controversies in the use of intravenous immunoglobulin therapy.

What this study adds?

Albumin levels and B/A ratio are the major factors of ET requirement and can be predictors of failure of IVIG treatment that it may be justified for elective use in neonates suffering from AIHDN.

Abbreviations

Alloimmune hemolytic disease of newborn (AIHDN)
American Academy of Pediatrics (AAP)
Bilirubin albumin ratio (B/A)
Direct antiglobulin test (DAT)
Exchange transfusion (ET)
Hemolytic disease of the fetus and newborn (HDFN)
Intravenous Immunglobulin **(**IVIG)
Neonatal intensive care units (NICU)
Phototherapy (PT)
Red blood cells (RBC).

Authors' contribution

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by [Gonca Vardar], [Meliha Aksoy Okan], [Nilgun Karadag], [Sevilay topcuoglu], [Elif Ozalkaya], [Hande Ozgun Karatepe], and [Guner Karatekin]. The first draft of the manuscript was written by [Gonca Vardar], and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University of Health Sciences Zeynep Kamil Maternity and Children's Research and Training Hospital. (Date 03.07.2018/No 31).

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Nil.

Conflicts of interest

There are no conflicts of interest.

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