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Intravenous immunoglobulin to treat hyperbilirubinemia in neonates with isolated Glucose-6-Phosphate dehydrogenase deficiency

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RESEARCH

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ABSTRACT

Background

Glucose-6-phosphate dehydrogenase deficiency alone or concomitant with ABO isoimmunisation is a widespread indication for neonatal exchange transfusion.

Aims

To evaluate the effectiveness of Intravenous Immunoglobulin in the treatment of neonatal hyperbilirubinemia due to glucose-6-phosphate dehydrogenase deficiency.

Methods

A retrospective cohort study was conducted between 2006 and 2014 at the Jordan University of Science and technology. The medical records of 43 infants admitted to the neonatal intensive care unit for isolated glucose-6-phosphate dehydrogenase deficiency hemolytic disease of the newborns were reviewed.

Patients were divided into two groups. Group I, a historical cohort, included newborns born between 2006 and 2010, Treatment included phototherapy and exchange transfusion. Group II included newborns born between 2011 and 2014, where, in addition to phototherapy, intravenous immunoglobulin was administered. The duration of phototherapy and number of exchange transfusions were evaluated.

Results

Of 412 newborns that were admitted with neonatal hyperbilirubinemia, Glucose-6-phosphate dehydrogenase deficiency was present in 43. Of these, 22, did not receive intravenous immunoglobulin and served as a control group. The other 21 newborns received intravenous immunoglobulin. There was no difference in the demographic characteristics between the two groups.
Infants in the control group were significantly more likely to receive exchange blood transfusion than infants in the immunoglobulin treatment group, but were significantly less likely to need phototherapy.

Conclusion

Intravenous immunoglobulin is an effective alternative to exchange transfusion in infants with glucose-6-phosphate dehydrogenase deficiency hemolytic disease of the newborn. It is suggested that intravenous immunoglobulin may be beneficial as a prophylaxis for infants with hyperbilirubinemia.

Key Words

Glucose-6-phosphate dehydrogenase deficiency, intravenous immunoglobulin, neonatal hyperbilirubinemia

What this study adds:

1. What is known about this subject?

This is the first report to demonstrate that intravenous immunoglobulin is effective in reducing the need for exchange blood transfusion in neonates with isolated glucose-6-phosphate-dehydrogenase deficiency.

2. What new information is offered in this study?

This study demonstrates the effectiveness of IVIG as an alternative to exchange blood transfusion for the management of neonatal hyperbilirubinemia with glucose-

6-phosphate dehydrogenase deficiency.

3. What are the implications for research, policy, or practice?

Glucose-6-phosphate-dehydrogenase deficiency is a leading cause for exchange blood transfusion, and this study demonstrated that Intravenous Immunoglobulin is an effective alternative.

Background

Worldwide, around 400 million people are estimated to be affected by glucose-6-phosphate dehydrogenase (G6PD) deficiency, which is the most common red cell enzymopathy.[1] A global prevalence of 4.9 per cent and a significant association with hyperbilirubinemia among neonates in the immediate perinatal stage are observed.[2,3]

It has been reported that deficiency of G6PD alone, or in association with ABO isoimmunization, to be a leading indication for exchange blood transfusion (EBT).[4]

Critical hyperbilirubinemia is considered a potential for the development of kernicterus or permanent neurological deficit.[5] The main factor for the development of neonatal hyperbilirubinemia is related to insufficient hepatic metabolism of unconjugated bilirubin, in place of increased hemolysis.[5-7] There is a high rate of EBT utilization in managing severe neonatal hyperbilirubinemia with significant morbidity.[8]

Immunoglobulins from human plasma were first used in 1952 to treat immune deficiency. Intravenous immunoglobulin (IVIG) contains more than 95 per cent unmodified immunoglobin G (IgG) products manufactured from pooled human plasma, and only trace amounts of immunoglobulin A (IgA) or immunoglobulin M (IgM).[9] The use of IVIG has been approved by the US Food and Drug Administration for the treatment of many diseases such as allogeneic bone marrow transplantation, chronic lymphocytic leukemia, immunodeficiency, hypogammaglobulinemia, chronic inflammatory demyelinating polyneuropathy.[9] It is approved for kidney transplant recipients with high antibody levels or ABO incompatibility, primary immunodeficiency disorders associated with defects in humoral immunity, immune-mediated thrombocytopenia, Kawasaki disease, hematopoietic stem cell transplantation in patients older than 20 years, chronic B-cell lymphocytic leukemia and pediatric HIV type 1 infection.[9]

The National Guideline Clearing House summarized the use of hematological IVIG to include the following conditions: aplastic anemia, pure red cell aplasia, Diamond-Blackfan anemia, autoimmune hemolytic anemia, hemolytic disease of the newborn, acquired factor VIII inhibitors, acquired Von Willebrand disease, immune-mediated neutropenia, refractoriness to platelet transfusion, neonatal thrombocytopenia, post transfusion purpura, thrombotic thrombocytopenia purpura, hemolytic uremic syndrome.[9]

Intravenous immunoglobulin is used to treat a variety of diseases in the neonatal intensive care unit (NICU).[10] Hemolytic disease of the newborn continues to be a common neonatal disorder. Common treatments include hydration and phototherapy. Exchange blood transfusion is used in severe cases, but is associated with many adverse effects. Intravenous immunoglobulin may have a place in this condition.[11] The use of intravenous immunoglobulin in isoimmune haemolytic disease due to ABO incompatibility is recommended by the American Academy of Pediatrics and the National Blood Authority, Australia. However, the evidence appears to be limited and, in some instances, controversial.[12]

In a study Demirel et al., IVIG therapy in combination with light emitting diode phototherapy in patients with neonatal jaundice secondary to ABO blood incompatibility did not affect exchange transfusion rates.[13] This is in concordance with a study by Smits-Wintjens et al., where prophylactic treatment with IVIG in rhesus hemolytic disease did not reduce the need for exchange transfusion or adverse neonatal outcomes.[14] However, in a study by Elelfy et al., IVIG administration was effective in reducing the duration of phototherapy and hospital stay in severe Rh hemolytic disease of the newborn.[15]

The aim of this study was to assess the effectiveness of IVIG as an alternative to EBT in infants with isoimmune haemolytic disease due to ABO incompatibility associated with isolated G6PD deficiency.

Method

The medical records of infants admitted to the neonatal intensive care unit (NICU) between January 2006 and December 2014 for isolated G6PD deficiency hemolytic disease of the newborn were reviewed. Common causes of pathological jaundice due to ABO or Rh isoimmunization, sepsis, hematoma, prematurity and hypothyroidism was considered.[16] Newborns were assessed every 4–6 hours for jaundice according to the Bhutani normogram.[17]

Extracted details included gestational age, birth weight,

presence of cephalhematoma, sepsis, maternal and baby blood group, direct Coombs test, thyroid function, peak bilirubin, length of hospital stay, use of IVIG and need for EBT.

Glucose-6-phosphate dehydrogenase Quantitative Enzyme Assay [Trinity^{R}, Biotech Kit NO 345, Wicklow, Ireland] was normalized using patients' hemoglobin according to manufacturer's instructions. We established the neonatal reference interval for G6PD to be set at 146 to 376 U/10-12 RBCs. When the enzyme level was <146 U/10-12 RBCs the diagnosis of glucose-6-phosphate dehydrogenase deficiency was confirmed.

During the period 2006-2010, treatment options were intensive phototherapy and exchange transfusion. Between 2011 and 2014, babies with elevated bilirubin, despite intensive phototherapy, received infusion of IVIG in a dose of 0.5–1g/kg of Intratect (Biotest Pharma Gmbh, Dreieich, Germany).

Number of IVIG infusions, need for top-up transfusions, and adverse events linked with treatment were recorded.

Data were analyzed using SPSS 16.0 (Statistical Package for the Social Science, SPSS INC. Chicago, IL, USA). Two-sided independent student t-test was used to analyze continuous data, and Fisher's exact test for categorical data. P value less than 0.05 was considered statistically significant for each comparison.

Results

During the study period, 412 infants were admitted with neonatal hyperbilirubinemia. Glucose-6-phosphate dehydrogenase deficiency was present in 43 newborns. Of these, 22 infants (Group I), did not receive IVIG and served as a control group. The other 21 (Group II), received IVIG (0.5-1gm/kg), administered over 2-3 hours.

There was no difference in the demographic characteristics between the two groups (Table 1).

Infants in Group I were significantly more likely to receive EBT than infants in Group II. Infants in Group II were significantly more likely to need phototherapy.

There was no significant difference in the need for top-up transfusions between the two groups (Table 1).

Discussion

The most common inherited enzyme deficiency among neonate is G6PD deficiency. This enzyme deficiency is associated with both neonatal hyperbilirubinemia and chronic hemolytic anemia. Acute hemolysis is elicited through exposure to oxidative stressors such as certain medications or infection.[18]

The highest prevalence rates of G6PD deficiency were reported among Sub-Saharan African countries, with a high degree of heterogeneity for regional and global prevalence estimates. Glucose-6-phosphate dehydrogenase deficiency is of public health import, particularly in planning programs to improve neonatal health.[18] In Jordan, G6PD deficiency affects approximately 10 per cent of newborns.[19] In a study of 336 neonates that underwent 386 EBTs, the most common indication for EBT, at 38.1 per cent was G6PD deficiency, either alone or concomitant with ABO incompatibility.[4]

Pharmacological treatments used to treat hyperbilirubinemia can speed up the normal metabolic pathways of bilirubin clearance and inhibit bilirubin formation by blocking heme degradation and hemolysis. Currently, IVIG is the only available treatment option for clinical use. The administration of IVIG to infants with isoimmune hemolytic disease will extensively reduce any need for exchange transfusions. The usual dose is 500mg/kg over 2–3 hours and, if necessary, repeated in 12 hours. Intravenous immunoglobulin is the first option treatment when total serum bilirubin rises despite intensive phototherapy or if it is within 2–3mg/dl of the exchange level.[20-22]

The frequent association of G6PD deficiency with severe neonatal hyperbilirubinemia requiring phototherapy and EBT is well established.[14,23] Research has confirmed that the introduction of IVIG, as a treatment option for rhesus hemolytic disease of the newborn, has reduced the need for EBT.[24,25]

To the best of the authors' knowledge, this is the first study of the effect of IVIG therapy in infants with hyperbilirubinemia due to G6PD deficiency, with the aim of reducing the rate of EBT.

Conclusion

Intravenous immunoglobulin is an effective alternative to exchange blood transfusion in infants with G6PD deficiency hemolytic disease of the newborn.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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Table1: Baseline variables of neonates with G6PD deficiency hemolytic disease

Variables	Group I (n=22)	Group II (n=21)	p-Value
Mean gestational age	35 weeks and 6 days	36 weeks	0.5948
Mean birth weight	2526 grams	2631 grams	0.6537
Mean bilirubin level (range)	247.95 µmol/L (119.7-328.3)	246.24 µmol/L (85.5- 415.5)	0.5750
Use of IVIG	0	21	0.0000
Need for exchange transfusion	14 (63.6%)	2 (9.5%)	0.0003
Top-up transfusion	0	1	0.4883
Mean phototherapy days (range)	4 (1-11)	7 (2-18)	0.0001