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The Role of Intravenous Immunoglobulins in Decreasing the Need for Exchange Transfusion in Neonates with Isoimmune Haemolytic Jaundice

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Abstract: Background: Neonatal Jaundice secondary to isoimmune haemolytic anemia (Rh and ABO incompatibility) is a cause of high serum bilirubin level due to haemolysis of red blood cells secondary to transplacental passage of antibodies. Intravenous immunoglobulins (IVIG) have been successfully used in isoimmune hemolytic jaundice and were found to decrease hemolysis leading to reduction in serum bilirubin level and subsequently decreasing the need for exchange transfusion. *Patients and methods:* This study was conducted on 30 full term neonates with isoimmune-hemolytic jaundice admitted in the neonatal intensive care units in New Children's hospital, Cairo University. They were randomly classified into 2 groups Group I: "Study group" (15) neonates presented with isoimmune hemolytic jaundice treated by phototherapy + single dose of I.V immunoglobulin infusion (0.5 gm/Kg). Group II: "Control group" (15) neonates presented with isoimmune-hemolytic jaundice treated by phototherapy only. Results: the rate of decrement in total serum bilirubin (TSB) was significant in the study group compared with the control group 24 and 48 hours after therapy where the P value was 0.000 and 0.001 respectively. The number of patients who required exchange transfusion was significantly lower in the study group than in the control group (P=0.007). *Conclusion:* intravenous immunoglobulins (IVIG) have been successfully used in newborns with isoimmune hemolytic jaundice. Routine use of Intravenous immunoglobulin therapy in treatment of isoimmune hemolytic jaundice plus conventional Phototherapy is recommended to decrease the need for exchange transfusion and avoid its complications.

Key words: Isoimmune hemolytic jaundice - IVIG.

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 3 days of life[1].

Neonatal Jaundice secondary to isoimmune haemolytic anemia (Rh and ABO incompatibility) is a cause of high serum bilirubin level due to haemolysis of red blood cells secondary to transplacental passage of antibodies. This leads to increased risk of bilirubin encephalopathy and kernicterus at bilirubin levels lower than that of jaundiced newborns without isoimmunisation or active haemolysis[2].

Regardless of the etiology, the goal of therapy is to lower the concentration of circulating bilirubin or keep it from increasing and reaching the levels at which neurotoxicity may occur[3].

The conventional treatment measures for neonatal immune hemolytic disease are Phototherapy and blood exchange. Phototherapy, converts bilirubin to products that can bypass the conjugating system and be excreted in the bile or the urine without further metabolism[3,4] Exchange transfusion removes bilirubin mechanically and is sometimes needed beside phototherapy as it corrects anemia associated with hemolysis and is effective in removing sensitised red blood cells before they are hemolysed. It also removes about 60% of bilirubin from the plasma. Exchange transfusion carries 5%risk of major morbidities including infections, apnea, pulmonary hemorrhage, thrombocytopenia, coagulopathies, hypoglycemia, hypocalcaemia, electrolyte imbalance, vasospasm, thrombosis, hypertension, arrhythmias, and necrotizing enterocolitis[5,6,7].

In isoimmune hemolytic diseases of the newborn, (Rh-ABO incompatibility), antibodies (Anti-A, anti-B, anti- D) coated erythrocytes are mainly eliminated through, antibody dependant cellular cytotoxic effect by Fc receptor bearing cells of the reticuloendothelial system[8].

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Intravenous immunoglobulins (IVIG) have been successfully used in isoimmune haemolytic anemia (Rh-ABO incompatibility); as its administration is a less complicated as well as less invasive therapy[9,10,11,12,13,14]. Intravenous Immunoglobulins were found to decrease hemolysis leading to reduction in serum bilirubin level. The exact mechanism of action of IVIG in hemolytic disease of the newborn is still unknown. The immunoglobulin could act by occupying the FC receptors of reticulo -endothelial cells preventing them from taking up and lysing antibody coated RBCs. This subsequently leads to decrease in the need for exchange transfusion[13,15,16]. Undesirable effects from IVIG occur in less than 5% of patients and include headache, flushing, chills, wheezing, tachycardia, low back pain, nausea and hypotension. If this happens during infusion, the infusion should be slowed or stopped; if symptoms are anticipated, the patient can be premedicated with antihistamines and intravenous hydrocortisone[17].

PATIENTS AND METHODS

Patients: This study was conducted on 30 neonates with isoimmune-hemolytic jaundice admitted in the neonatal intensive care units in New Children's hospital, Cairo University. They were randomly classified into 2 groups:

Group I: "**Study group**" (15) neonates presented with isoimmune hemolytic jaundice treated by phototherapy + single dose of I.V immunoglobulin infusion (0.5 gm/Kg).

Group II: "**Control group**" (15) neonates presented with isoimmune-hemolytic jaundice treated by phototherapy only.

Both groups were compared with each other regarding the rate of decrement in serum bilirubin, duration of phototherapy and number of babies required exchange transfusion.

Term neonates (≥ 37 weeks gestational age) with isoimmune hemolytic jaundice due to Rh or ABO incompatibility between blood group of the mother and the baby ,proved by Positive direct Coomb's test and clinical jaundice in the first 36 hours of life were included in the study.

Significant hyperbilirubinemia; was defined as hyperbilirubinemia requiring phototherapy and/or rising by (0.5mg/dl per h) or if the total serum bilirubin level exceed (10 mg/dl), (12 mg/dl), (14 mg/dl) at <12hr, <18hr or <24hr of the infant age respectively[18].

Preterm neonates, neonates with infections, hematomas, gastrointestinal abnormalities as well as pathological conditions other than isoimmune haemolytic jaundice e.g. (respiratory distress syndrome and intrauterine growth retardation) were excluded from the study.

All the studied cases (Group I and Group II) were subjected to the following:

(A) Clinical Evaluation:

1-History taking (complete obstetric and medical history of the mother stressing on prenatal, natal, and postnatal history)

2 -Thorough clinical examination including:

General examination: (vital signs, birth trauma, neonatal reflexes, and congenital anomalies).

Systemic examination : (cardiac, abdominal, chest and neurological examination,

B) Phototherapy: each neonate was placed naked body, covering the eyes and genitalia, at distance of 30-40 cm from the light source in an incubator and was managed with continuous phototherapy.

(C) Laboratory Investigations: serum bilirubin level (total and direct), direct coomb's test, reticulocytic count and complete blood count.

Intravenous Immunoglobulin: The neonates were treated by 0.5 gm/kg single dose of I.V-Globulin S (Heat-treated Immune Serum Globulin) at the time of admission through intravenous (I.V) infusion over 4 hours at a rate of 0.01mg/kg/minute (for group I only)[17]. Estimation of serum bilirubin was done after 4 hours from termination of infusion and then every 24 hours. No adverse reactions have been observed in the studied patients.

Statistical Analysis: SPSS program (version 12) was used in the statistical presentation and analysis of the present study using the mean, standard error, unpaired student t-test, chi-square test and the Mann-Whitney test.

RESULTS

In this work thirty neonates suffered from neonatal jaundice due to Rh or ABO incompatibility were studied; they were divided into two groups. ***Group I*** (treated group or the study group) and ***Group II*** (control group or the non treated group).

The general characteristics and laboratory data of both groups are presented in (Table 1) and showed no significant statistical difference between them ($p>0.05$). These characteristics included the gestational age (weeks), birth weight (grams), type of isoimmunization (Rh or ABO), family history of neonatal jaundice, onset of jaundice (days) and age of admission (hours). In each group 14 patients had ABO incompatibility;

Table 1: General characteristics and laboratory data of both groups.

	Group I	Group II	t-test	P value
Gestational age (Weeks)	37.93±0.961	37.8±0.775	0.42	0.68
Birth weight (grams)	3040±324.7	3033.33±330.94	0.056	0.95
Family history with other child with jaundice	6 (40%)	4 (26.67%)		0.35
Onset of jaundice (days)	1.27±0.46	1.4±0.5	- 0.76	0.46
Age of admission (hours)	35.13±20.9	37.93±22.2	- 0.36	0.72
HB level (g/dl)	12.1±1.45	12.22±2.25	- 0.16	0.87
Reticulocytic count	11.04±4.75	10.19±8.3	0.35	0.73
Hematocrite percent	36.5±4.98	34.96±6.48	0.73	0.47

Table 2: Total serum bilirubin (TSB) in Group I and Group II 24 hours and 48 hours from therapy.

TSB(mg/dl)	Group I	Group II	t- test	P value
On admission	13.6-31.1	14.00-30.90		
	18.747±4.474	21.458±5.346	-1.506	0.143
24 hours	10.80-25.00	15.12-29.90		
	15.833±3.736	22.527±4.380	-4.503	0.000*
48 hours	6.70-29.10	15.70-30.00		
	13.120±5.293	18.879±3.409	-3.543	0.001*

*P>0.001 is highly significant .

Table 3: The change in Total Serum Bilirubin (TSB) in both groups 24 hours and 48 hours after therapy as compared with the initial value on admission.

Group		TSB	t- test	P-value
Group I	On Admission	13.60-31.10		
		18.747±4.474	0.421	0.680
	After 24h.	10.80-25.00		
		15.833 ± 3.736	3.314	0.005*
	After 48h.	6.70- 29.10		
		13.120±5.293	4.560	0.000*
Group II	On Admission	14.00-30.90		
		21.458 ± 5.346	-0.860	0.404
	After 24h.	15.12-29.90		
		22.527± 4.380	1.630	0.125
	After 48h.	15.70-30.00		
		18.879 ±3.409	3.144	0.007*

* P>0.05 is significant .
* P>0.001 is highly significant.

Table 4: Frequency of exchange transfusion in both groups

Group		Ex. transfusion		
		No	Yes	Total
Group I	N	14	1	15
	%	93.33	6.67	100.00
Group II	N	7	8	15
	%	46.67	53.33	100.00
Total	N	21	9	30
	%	70.00	30.00	100.00
Fisher's exact test		0.007		

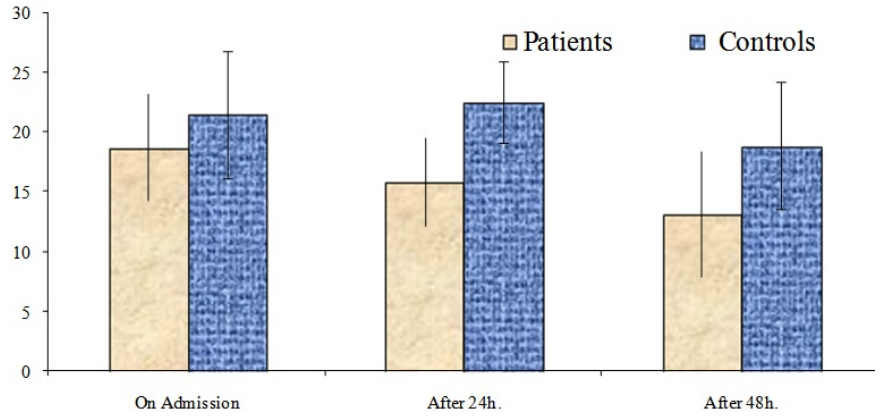

Fig. 1: Rate of Decrement in Total Serum Bilirubin in Both Groups 24 Hours and 48 Hours after Therapy.

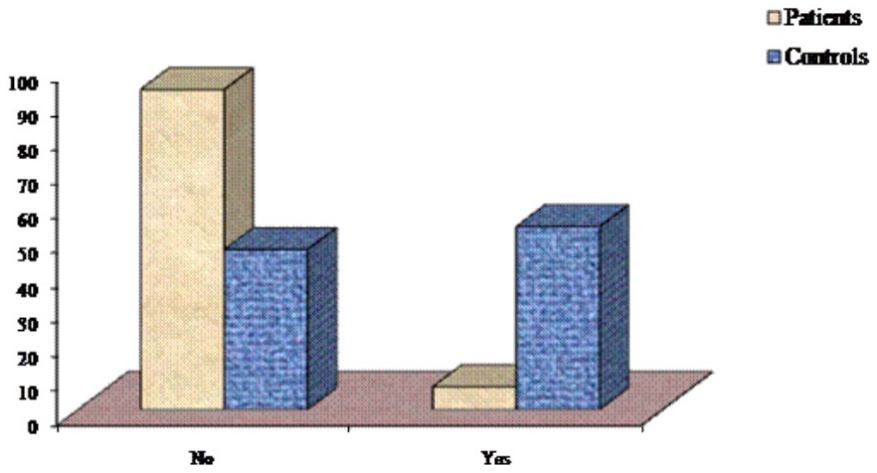

Fig. 2: Frequency of Exchange Transfusion in Both Groups.

Rh+ ABO was present in 1 patient in each group and none of the patients had Rh incompatibility alone in both groups. The laboratory data included the hemoglobin (HB) level (g/dl), Reticulocytic count and hematocrite (Hct %) percent and showed no significant statistical difference between **(Group I)** and **(Group II)** ($p>0.05$).

The rate of decrement in the total Serum Bilirubin (TSB) in Both Groups 24 Hours and 48 Hours after Therapy is presented in (table 2 and fig.1) which show that There was no significant statistical difference between **(Group I)**and **(Group II)** in (TSB) level on admission($p>0.05$); while after24 and 48 hours of therapy the (TSB) level was significantly lower in the treated group **(Group I)** than the control group **(Group II)** where the p value was 0.000 and 0.001 respectively.(Table 3) displays the change in (TSB) in Both Groups 24 Hours and 48 Hours after Therapy as compared with the initial value on admission and shows that there was significant statistical difference between (TSB) after 24 hours and 48 hours in **(Group I)**($p=0.005$ and 0.000 respectively) and a significant statistical difference in (TSB) after 48 hours only in **(Group II)**($p=0.007$).

Regarding the duration of phototherapy the difference was not statistically significant ($p>0.05$) in both groups where in the patient group the mean duration was (85.07±24.33 hours) and in the control group the mean duration was (96.33±20.48 hours).

(Table 4 and fig.2) present the frequency of exchange transfusion in both groups where the number of patients who required exchange transfusion was significantly higher in the control group **(Group II)** than in the study or treated group **(Group I)** ($p=0.007$).

DISCUSSION

Hemolytic jaundice caused by blood group incompatibility has significant morbidity and mortality

in neonatal period. It is accepted that introduction of anti-D for prophylaxis of Rh incompatibility reduces the number of cases with hemolysis. However, because the prophylactic anti-D treatment cannot often be given in time or in adequate dosage, Rh hemolytic disease remains an important problem of neonates, furthermore, there is no prophylactic treatment for ABO or Rh subgroup incompatibilities. The conventional therapy for this disease is phototherapy, hydration and exchange transfusion. [13]

Intravenous immunoglobulin (IVIG) therapy is now used in the treatment of Hemolytic disease of the newborn (HDN). They reduce the need for exchange transfusion, duration of hospitalization, and phototherapy. [12, 13]

In our experience we studied the effect of a single dose of IVIG therapy (500mg/kg) on neonates with isoimmune hemolytic jaundice; which was in concordance with other studies [14, 19] in which the effect of a single dose of IVIG (500 mg/kg) on term and preterm neonates was examined. In other reports[20,21,22] different dose regimens of IVIG (1g/kg and 800mg/kg) were also tried in neonates with isoimmune hyperbilirubinaemia. Some authors systematically reviewed the effect of intravenous immunoglobulins in hemolytic disease of the newborn, comparing four controlled trials on 226 neonates and all the studies included showed a beneficial effect, despite the variation in IVIG doses. They suggested that a single dose of 500 mg/kg is as effective as any other treatment regimen[13].

Agreeing with other results[12,14] we found no significant statistical difference between both groups concerning gestational age, birth weight; as well as the hemoglobin level, reticulocytic count and the initial level of serum bilirubin.

In accordance with other studies[9,23] we proved that there was a highly Significant decrease in the number of cases who needed exchange transfusion in the group treated with IVIG (15 patients) where only one of them (6.67%) required exchange transfusion in view of 7 cases (46.67%) of the control group (15 patients) who were in need for exchange transfusion. (p<o.o1)

Supporting our findings, many authors[9,14,19] studied the effect of a single dose IVIG (500mg/kg) on neonates with significant hyperbilirubinaemia due to ABO and Rh hemolytic disease and their results showed a significant decrease in the number of cases in need for exchange transfusion in the treated group compared with the control group where the P value was <0.005, <0.01 and <0.05 respectively. Previous studies[12] examined the effect of multiple doses (500 mg/kg) IVIG therapy during 3 consecutive days versus single dose (500 mg/kg) IVIG therapy on neonates with isoimmune hemolytic hyperbilirubinemia The rate of exchange transfusion in multiple doses IVIG treated group, was lower than the single dose IVIG treated group (P<0.01).Also the rate of exchange transfusion in the single dose IVIG treated group was lower than the control group babies who didn't receive any IVIG (P<0.05).

In keeping with other reports[9,19]; our experience showed no statistically significant difference in the duration of phototherapy in the treated group (mean 85.067±24.33hours) compared with the control group babies who had only phototherapy (mean 96.33_+20.48 hours). (P>0.05)

We reported no immediate adverse effects related to IVIG including fever, allergic reactions, volume overload or hemolysis, which agreed with the findings observed by many authors who detected no immediate adverse effects related to IVIG[11,12,14,19,21,22].

In conclusion intravenous immunoglobulins (IVIG) have been successfully used in newborns with isoimmune hemolytic jaundice; our results showed significant decrease in the number of cases in need for exchange transfusion, in the treated group more than the control group (P value < 0.01). Routine use of Intravenous immunoglobulin therapy in treatment of isoimmune hemolytic jaundice plus conventional Phototherapy is recommended to decrease the need for exchange transfusion and avoid its complications. Further studies are also needed to determine the best regimen in Intravenous immunoglobulin therapy, single dose versus multiple doses, the dose itself and the best time for initiation of therapy.

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