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RHESUS HEMOLYTIC DISEASE OF THE NEWBORN

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ABSTRACT

Background: Hemolysis, anemia, and jaundice in newborns are all frequently brought on by Rhesus Hemolytic Disease of the Newborn due to Rhesus Incompatibility (HDN-Rh), a prevalent pediatric condition that increases morbidity and death in kids. **Aim of thee study:** To have an idea about rhesus hemolytic disease, severity and its problems in addition to efficacy of anti-D immunoglobulin and efficacy of phototherapy in preventing further exchange transfusion, and to find out whether ABO incompatibility is protective or not. **Patients and Methods:** A case-control study design was chosen to achieve the study objectives and the sample consisted of 50 patients and 50 controls collected from those who were admitted to the AL-Khansaa Teaching Hospital in Mosul city during the period from the first of August, 1999 to the 31 of Jan., 2000. Clinical data include parity, gestational age, sex, the presence of previous hemolysis or previous abortions, administration of anti D antibody by the mother previous blood transfusion to the mother, the presence of jaundice and the time of onset, and d the presence of pallor. **Results:** Thirty four of the patients were males (68.0%) and 16 were females (32.0%); male to female ratio was 1:1.875. the control group consisted of 27 males (54.0%) and 23 females (46.0%) and male to female ratio was 2.1:1. The proportion of full term in patient group was 37(74.0%) and in control group 35(70.0%), but the incidence of preterm in patients group was 13(26.0%) and in control group 15(30.0%). The proportion of severe rhesus hemolytic disease and the need for exchange transfusion were more in multiparous women ($p<0.013$). Previous hemolysis was found in the 27 treated patients and 23 untreated patients of Rh incompatibility group and it was shown that the number of treated patients who had previous hemolysis was 9(33.3%) and in untreated patients were zero ($p<0.002$), so the incidence of previous hemolysis was just significant. The proportion of previous hemolysis in phototherapy and exchange transfusion group showed highly significant difference. The comparison of Anti D administration between treated and untreated groups revealed that not given Anti D carried 7.5 times risk for development of disease with a statistically significant association ($p<0.002$). The Comparison of ABO incompatibility in the treated and untreated groups showed that the presence of ABO incompatibility was not protective. **Conclusion:** Hemolytic disease of newborns due to Rh-incompatibility remains as a serious issue in our country, causing morbidity and mortality because of shortage of anti-D antibodies, ignorance and careless from the side of family. Hemolytic disease of newborns due to Rh-incompatibility could be prevented by Anti-D immunoglobulin.

KEYWORDS: Hemolytic Disease, Newborn, Rhesus-incompatibility.

INTRODUCTION

Hemolysis, anemia, and jaundice in newborns are all frequently brought on by Rhesus Hemolytic Disease of the Newborn due to Rhesus Incompatibility (HDN-Rh), a prevalent pediatric condition that increases morbidity and death in kids. Although the development of a way to prevent maternal iso-immunization by Rh antigens, HDN-Rh, also known as iso-immune hemolytic disease of the newborn, persists to be a significant cause of anemia as, well as, jaundice in newborn infants. It is caused by the trans-placental crossing of Rh-ve maternal blood that contains antibodies active against Rh +ve red blood cell antigen of the neonates.[1]

When Rh +ve blood is accidentally infused and mixed with Rh -ve women or when little amounts (typically more than 1 ml) of Rh positive fetal blood containing D

antigen inherited from a Rh +ve father enter the maternal circulation during pregnancy, with spontaneous or induced abortion, or delivery, antibody formation against D may be induced in the mother. This condition is known as iso-immune hemolytic disease from D antigen and is about three times more common in whites than in blacks.[1,2] After immunization, much lower doses of antigen can still cause an increase in antibody titer; at first, 19s gamma globulin fraction antibody levels rise, but this is soon replaced by 7s (IgG) antibody, which easily crosses the placenta and results in hemolytic manifestation (2). The Rh antigenic determinants, which are genetically passed down from each parent and determine the Rh type as well as the production of several blood group factors (C, c, D, d, E, and e), can each, under the right circumstances, elicit a particular antibody response, with 90% of these responses being caused by the D antigen and the remaining 20% by C or E (1). In pre-transfusion testing, the distinction between anti-D, anti-C, and anti-C species is rarely thought to be clinically significant.[2]

Since transfusions of Rh positive fetal blood into Rh negative mothers typically take place close to birth, it is uncommon for hemolytic illness to develop during a first pregnancy because the mother cannot acquire sensitized and cannot pass antibodies to the baby prior to delivery.[1]

The fact that 55% of Rh +ve fathers are heterozygous (D/d) and may have Rh negative offspring and that only 50% of pregnancies have fetal-to-maternal transfusion reduces the chance of sensitization as does small family size, in which he opportunistic for its occurrence arc fewer; finally, the capacity of Rh -ve woman to form antibodies is variable, some producing low titers even after adequate antigenic challenge; thus, the overall incidence of iso-immunization of Rh -ve mothers at risk is low, with antibodies to D detected in less than 10% of those studied, even after five or more pregnancies, only about 5% ever have babies with hemolytic disease when mother and fetus are incompatible with respect to group A or B, the mother is partially protected against sensitization by the rapid removal of Rh +ve cells from her circulation by her anti-A or anti-B which are IgM antibodies and do not cross the placenta; once the mother has been sensitized, the infant is likely to have hemolytic disease.[1-3]

Fetal erythrocytes may be sufficiently coated for splenic or hepatic reticuloendothelial cells to lyse or phagocytose them.[3] The likelihood that the first affected child after sensitization may represent the end of the mother's capacity to bear Rh +ve infants makes it imperative to prevent sensitization when this is possible. One method of prevention is to administer anti-D gamma globulin (RhoGAM) to the mother as soon as each Rh +ve baby is delivered.[1]

Hyperdynamic circulation in both venous and arterial vessels is linked to anemia and heart failure.[4] Erythroblastosis fetalis, also known as hydrops or widespread edema, and heart failure caused by severe anemia in the fetus can occur in extreme cases.[5]

Without proper antenatal care, hydrops frequently results in fetal or newborn death; in milder situations, hemolysis is the predominant issue, leading to hyperbilirubinemia and anemia.[5] Both hemolysis of newly produced erythrocytes by circulating antibodies, which normally last for more than a month after birth, and inhibited erythropoiesis may contribute to the intrauterine and postnatal anemia in fetuses who received intrauterine transfusions.[6] Iron excess and cobalamin insufficiency are linked to fetal hemolytic anemia.[7]

Factors that increase the retention of bilirubin in the circulation (hypoproteinemia, displacement of bilirubin from its binding sites on albumin by competitive binding, such as acidosis, increased fatty acid concentration as a result of hypoglycemia, starvation, hypothermia, or drugs such as sulfisoxazole and moxalactam, although moxalactam cause a linear increase in bilirubin levels) increase.[1] Dehydration increases the serum levels of bilirubin; meconium has 1 mg of bilirubin and may contribute to jaundice by the enterohepatic circulation after being deconjugated by intestinal glucuronidase; drugs like oxytocin and chemicals may produce jaundice as well as other risk factors that increase the permeability of the blood brain barrier or nerve cell membrane to bilirubin or increase the susceptibility of the brain cells to its toxicity.[1.9]

Study's objectives

1. To have an idea about rhesus hemolytic disease, severity and its problems.
2. To find out whether ABO incompatibility might be prevented or not.
3. To find out the effectiveness of anti-D immunoglobulin.
4. To find out the effectiveness of phototherapy in preventing further exchange transfusion.

PATIENTS AND METHODS

Fifty patients whom their mothers were rhesus negative admitted to the AL-Khansaa Teaching Hospital in Mosul city were studied during the period from the first of August, 1999 to the 31 of Jan., 2000. Males were 34 while females were 16; their age ranged from 1-10 days.

They were divided into two groups

Group 1: Consisted of 28 patients for those who presented early in the first 6 hours of life.

Group 2: Consisted of 22 patients for those who presented late after the first 6 hours of life.

Other fifty healthy patients (age and sex matched) whom their mothers were rhesus positive were taken as a control group (27 males) and (23 females).

Clinical data include parity, gestational age, sex, the presence of previous hemolysis or previous abortions, administration of anti D antibody by the mother previous blood transfusion to the mother, the presence of jaundice and the time of onset, and d the presence of pallor.

All the babies were examined systematically for the existence of jaundice, pallor, and organomegaly and any sign of kernicterus, in addition to determination of maturity and gestational age. Then, we did the investigations for the babies, as following:

Hemoglobin (Hb) with retics count, blood group and Rh in addition to total serum bilirubin (TSB) and direct coombs test. For the mother, the following investigations were done: Blood group and Rh, and indirect coombs test. And according to the history of the mother, siblings, the present and previous pregnancies with the investigations we found that some of the patients did not need treatment and others needed treatment which was either exchange transfusion (ET) with phototherapy (group B) or phototherapy alone (group A), according to their general condition and investigations. Then we had to do the statistical tests which were done to find the relationship between group 1 and 2 and also between groups A and B. These statistical tests include Z, T test, P values (significance), and the relationship (*r*). Also, the mean and standard deviation were calculated for the Hb, TSB, and retics count values for each group and compared with the other group. For the control group, Hb and total serum bilirubin were estimated.

RESULTS

Thirty four of the patients were males (68.0%) and 16 were females (32.0%); male to female ratio was 1:1.875. the control group consisted of 27 males (54.0%) and 23 females (46.0%) and male to female ratio was 2.1:1 as shown in figure (1).

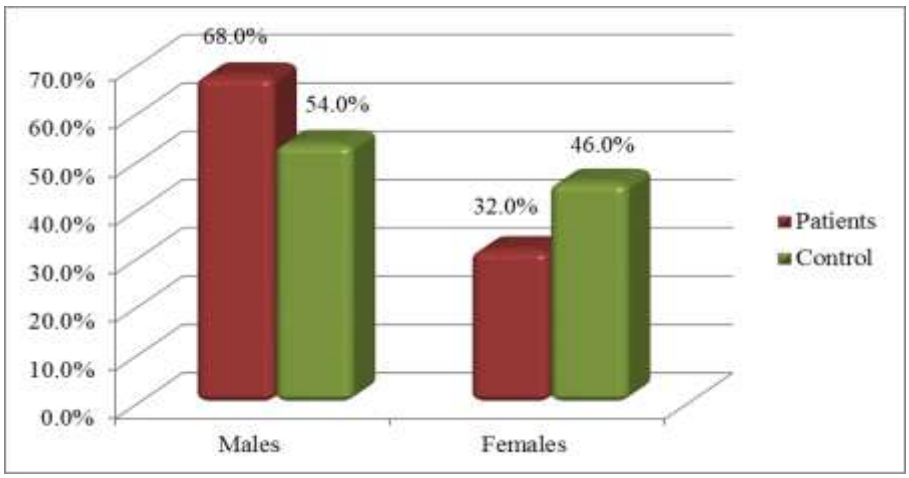

Figure 1: Distribution of study groups according to sex.

The proportion of full term in patient group was 37(74.0%) and in control group 35(70.0%), but the incidence of preterm in patients group was 13(26.0%) and in control group 15(30.0%), as shown in figure (2).

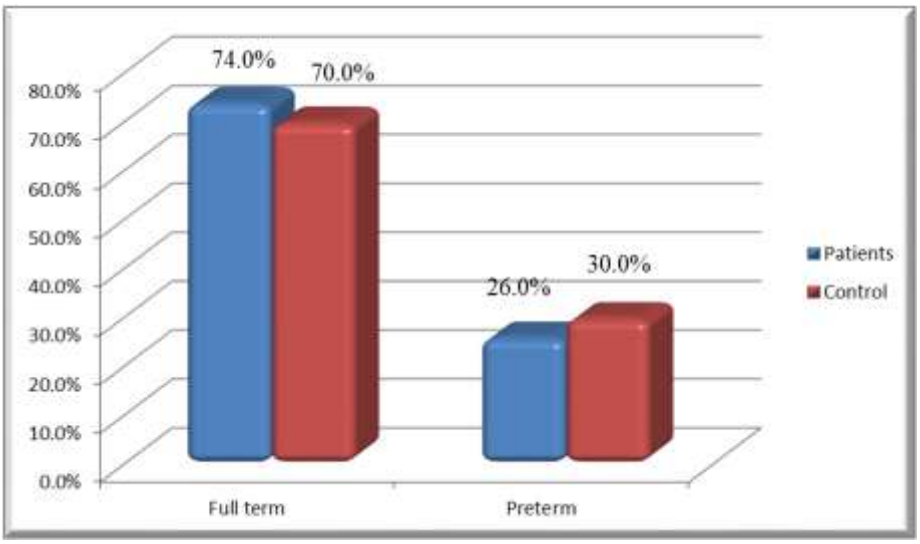

Figure 2: Distribution of full term and preterm in the study groups.

The proportion of severe rhesus hemolytic disease and the need for exchange transfusion were more in those who was more in those who where multiparous women (p<0.013) as shown in table (1).

Table 1: Relationship of Hemolysis to Parity of Mothers.

Groups	Total No.	Gravida >5		Gravida <5		p-value *
		No.	%	No.	%	
Exchange transfusion group	10	7	70.0	3	30.0	**0.013**
Phototherapy group	17	3	17.6	14	82.4	
*Fisher Exact test has been used						

Table (2) showed the distribution of blood group in mothers and their babies and demonstrated that the most frequent blood group was O and the least group was AB.

Table 2: Distribution of Different Blood Groups in The Mothers and Babies In Rh Incompatibility Group.

Blood groups	No. of mother	Percentage of mother	No. of babies	Percentage of babies
A	9	18	11	22
B	12	24	16	32
AB	3	6	6	12
O	26	52	17	34

Previous hemolysis was found in the 27 treated patients and 23 untreated patients of Rh incompatibility group and it was shown that the number of treated patients who had previous hemolysis was 9(33.3%) and in untreated patients were zero (p<0.002), so the incidence of previous hemolysis was just significant as shown in table (3).

Table 3: Comparison of Previous Hemolysis Between Treated and Untreated Groups.

Previous hemolysis	Treated (n=27)	Untreated (n=23)	OR	p-value *
	No. (%)	No. (%)		
Absent	18(66.7)	23(100.0)	0.000	**0.002**
Present	9(33.3)	0(0.0)		
*Fisher Exact test has been used				

The incidence of previous hemolysis in phototherapy and exchange transfusion group (p<0.003) was demonstrated in table (4) and showed highly significant difference.

Table 4: The incidence of Previous Hemolysis in Phototherapy Group and Exchange Transfusion Group.

Previous hemolysis	Phototherapy group (n=17)	Exchange transfusion group (n=10)	OR	p-value *
	No. (%)	No. (%)		
Absent	15(88.3)	3(30.0)	17.5	**0.003**
Present	2(11.7)	7(70.0)		
*Fisher Exact test has been used				

The comparison of Anti D administration between treated and untreated groups was demonstrated in table (5) and revealed that not given Anti D carried 7.5 times risk for development of disease with a statistically significant association (p<0.002).

Table 5: The comparison of Anti D Administration Between Treated and Untreated Groups.

Anti D administration	Treated group (n=27)	Untreated group (n=23)	OR	p-value *
	No. (%)	No. (%)		
Not given	23(85.2)	10(43.5)	7.475	**0.002**
Given	4(14.8)	13(56.5)		
*Chi square test has been used				

The Comparison of ABO incompatibility in the treated and untreated groups was shown in table (6), which showed that the presence of ABO incompatibility was not protective and not significant.

Table 6: The Comparison of ABO Incompatibility Between the Treated and Untreated Groups.

ABO incompatibility	Treated group (n=27)	Untreated group (n=23)	OR	p-value *
	No. (%)	No. (%)		
Absent	20(74.1)	16(69.6)	1.25	0.723
Present	7(25.9)	7(30.4)		
*Chi square test has been used				

Table (7) showed the distribution and incidence of jaundice, pallor, and family history of previous hemolysis in Rh incompatibility and its subgroups which shows that all the patients who required exchange transfusion (group B, n=10) had jaundice and pallor in the first day, and most of them had previous history of hemolysis and 4 of them had features of kernicterus, and the majority of those who were treated with phototherapy only (group A, n=17) had jaundice only and no pallor, and only 2 of them had previous history of hemolysis. No one of control group showed jaundice, pallor or family history of previous hemolysis. While 32 of patient group showed jaundice, 12 showed pallor and 9 had history of previous hemolysis.

Table 7: Distribution of Jaundice and Pallor in Rh Incompatibility Patients and Its Subgroups.

Groups	No.	Jaundice		Pallor		Previous hemolysis	
		No.	%	No.	%	No.	%
Total patients group	50	32	64.0	12	24.0	9	18.0
Treated patients group	27	26	96.2	12	44.4	9	33.3
Untreated patients group	23	6	26.1	0	0.0	0	0.0
Group A	17	15	88.2	0	0.0	2	11.7
Group B	10	10	100.0	10	100.0	7	70.0
Group 1	28	15	53.5	4	14.2	1	3.5
Group 2	22	16	72.7	7	31.8	8	36.3

The comparison of hematological findings showed in table (8) and demonstrated that the mean and standard deviation of hemoglobin, reticulocyte count, and total serum bilirubin between the patients and the control groups.

Table 8: The Comparison of Hematological Findings.

Hematological	Patients group (n=50)		Control group (n=50)		p-value *
	Mean	SD	Mean	SD	
Hb	15.97	3.973	17.49	1.429	0.088
Retic	6.88	7.25	2.79	0.8	**0.01**
TSB	5.79	6.381	1.18	0.349	**0.001**
*t-test for independent two means					

The comparison of hematological findings showed in table (9) and demonstrated that the mean and standard deviation of hemoglobin, reticulocyte count, and total serum bilirubin between the exchange transfusion group and the phototherapy groups.

Table 9: The comparison of Hematological Findings Between Exchange Transfusion and The Phototherapy Groups.

Hematological	Exchange transfusion group (n=10)		Phototherapy group (n=17)		p-value *
	Mean	SD	Mean	SD	
Hb	9.0	1.708	15.90	1.320	**0.001**
Retic	13.57	3.390	6.34	2.337	**0.001**
TSB	14.91	10.080	6.39	4.58	**0.006**
*t-test for independent two means					

The comparison of hematological findings between group 1and 2 demonstrated in table (10) and revealed statistically significant difference regarding the TSB only.

Table (10): The Comparison of Hematological Findings Between Group 1and 2.

Hematological	Group 1 (n=28)		Group 2 (n=22)		p-value *
	Mean	SD	Mean	SD	
Hb	16.53	2.995	14.29	8.42	0.197
Retic	5.36	4.056	4.13	5.80	0.382
TSB	3.03	1.764	10.77	8.73	**0.001**
*t-test for independent two means					

DISCUSSION

It was showed that ET was more necessary for the neonates of multiparous (p 0.001), therefore the severity of hemolysis will be raised when the parity of the mothers increases, as well. Due to fetomaternal transfusion occurring with each pregnancy and the sickness being worse with subsequent pregnancies, Swinhoe *et al.*,[10] demonstrated this discovery in 1990.

History of prior hemolysis: We discovered that 7 out of 10 patients who needed exchange transfusions also had siblings who had previously experienced hemolysis, although only 2 of the 17 patients who needed phototherapy did. This indicates that treatment is required since the severity of the current hemolysis is increased by the presence of past hemolysis (p 0.001). In contrast, none of the untreated group's (23) members (p 0.05) had a history of prior hemolysis. Consideration of prior kernicterus or severe erythroblastosis fetalis in a sibling is an additional element when deciding on treatment, rather than merely basing the choice on the severity of anemia and/or hyperbilirubinemia.[1]

Thirteen out of 23 patients were non-treatment candidates. Their mothers were given an anti-D IG in a single dose, this dose was efficient in avoiding hemolysis in subsequent carriages (p 0.01), which is why their babies didn't need any treatment. This finding is consistent with those made by Swinhoe *et al.*,[10], Whitfield *et al.*,[11], the Dijk study[12], and Joseph & Kramer.[13] It may be more beneficial to administer anti-D antibody during 28 to 32 weeks of gestation in addition to another dosage at delivery within 72 hours of delivery since fetomaternal blood transfusions can occasionally be considerable.[1]

Only four of the remaining 27 mothers who needed to be treated for their infants received a single dose of anti-D antibodies. Immunoprophylaxis has failed to provide protection against rhesus sensitization, according to Hundric *et al.*'s[14], Portmann *et al.*'s.[15], and Pereira & Bergstrom's [16] studies. Hundric et al. also found that the advantage of anti-D immunoglobulin for prophylaxis against rhesus alloimmunization was insufficient after abortions and multiple pregnancies.

In this investigation, it was discovered that the patients' mothers' ABO incompatibility did not provide considerable protection against hemolysis. ABO incompatibility between the mother and her unborn child should not considered in a decision regarding treatment, according to Bowmann study[17], which also found that once erythroblastosis fetalis has developed following rhesus immunization, ABO incompatibility does not affect how severe it is. The quick elimination of the fetal RBCs by IgM anti-A and anti-B antibodies of the mothers which not passing through the placenta, is one way that ABO incompatibility protects against rhesus hemolysis.[1]

While no such evidence was found in the control group, clinical signs of hemolysis such as pallor and jaundice were present in 64% and 24% of neonates, in that order. This indicates that Rh-incompatibility is a risk of hemolysis. Moreover, the confirmation of hemolysis was obvious in the neonates group which required ET than who only received phototherapy.

There was a noticeable amount of hemolysis in the patient group, as evidenced by the significant difference in Hb between the patient group and control group (p0.05), as well as the significantly different levels of bilirubin and reticulocyte count between the patient group and control group (p <0.001). Hb and TSB, the two main markers of hemolysis, were significantly correlated in the patient group (r= - 0.564, p<0.001) but not in the control group (r= 0.018). This result was also found by Hayde *et al.*,[18] in 1997, which means that hemolysis occur in the rhesus incompatibility and not in the control group. The variation in the Hb-value and retics count was highly significant (p< 0.001) between those patients who required ET and those who needed phototherapy only (i.e. lower Hb-value and higher retics count in the first set than the second). The mean hemoglobin in ET group was below 10 gm/dL, additionally, TSB value was higher among the group who required ET than those who needed phototherapy only (p<0.001). All the previously mentioned results point out that hemolysis in the ET group was more severe in comparing with phototherapy group.

Due to the high level of maternal antibodies against the newborns' +Rh RBCs, the direct Coombs test was positive in all the babies who needed exchange transfusions, while it was negative in the phototherapy group. This test is a weak marker for hemolysis, which was also demonstrated by Swinhoe *et al.*[10] in 1990. It is also a fact that maternal antibodies to D.-antigen are detected in less than 10% of the mothers.[1] Only 2 mothers, or 4%, had positive indirect Coombs' tests, and their babies had hydrops fetalis and died soon after birth.

Twenty-seven patients needed medical attention; 10 of them required exchange transfusions (20.0%), primarily because their TSB was extremely high and their hemoglobin level was below 10 g/dl, and 17 of them required phototherapy (34%). Additionally, Filbey *et al.*[19] discovered in 1997 that 22.2% of his kids needed exchange transfusions in their trial. This result was also found by DIjK in his study on the efficacy of phototherapy as a substitute for exchange transfusion particularly in severe hemolysis and came out to the suggestion that phototherapy is not a reliable substitute for exchange transfusion.[12] Phototherapy was only used in milder cases, and it was discovered that phototherapy in severe cases did not reduce the need for further exchange transfusion. One exchange transfusion was sufficient for four of the ten patients who needed it since they arrived early; however, four of the other six patients, who arrived late, required multiple exchange transfusions.

CONCLUSION

1. Earlier detection and treatment of the disease may diminish its complications as kernicterus, the late presentation was because of the ignorance of the family as either they give the baby glucose water instead of the milk or putting him or her under the Florissant light.
2. Hemolytic disease of newborns due to Rh-incompatibility remains as a serious issue in our country, causing morbidity and mortality because of shortage of anti-D antibodies, ignorance and careless from the side of family.
3. Hemolytic disease of newborns due to Rh-incompatibility could be prevented by Anti-D immunoglobulin.

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