

## **The prevalence of the ABO hemolytic disease of the newborn and its complications in an Iranian population**

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### **Abstract**

**Background:** ABO incompatibility is the most common cause of immune hemolytic disease of the newborn (HDN) and in most cases is not dangerous. The present study aimed to determine the prevalence of ABO-HDN and its effects on neonatal blood parameters in a population of patients referred to some training hospitals in Iran.

**Materials and methods:** In This cross-sectional study, All newborns (a total of 765 infants) whose medical records showed that they suffered from anemia or jaundice and were hospitalized in the training hospitals of Khorramabad, Iran, were evaluated. The information recorded in their medical records included age, gender, blood group, hemoglobin and bilirubin levels, reticulocyte count, platelet count, and maternal age. Data were analyzed using SPSS and statistical tests, such as chi-squared, independent t-test, and the Mann-Whitney test.

**Results:** Out of 765 newborns with anemia or jaundice, 293 infants (38.3%) had HDN, 78 (10.2%) of whom suffered from non-immune HDN. The rest, i.e. 215 neonates (28.1%), suffered from immune HDN. Among the neonates with immune HDN, 29 infants (3.8%) had Rh-HDN, and 186 newborns (24.3%) had ABO-HDN. Among the 186 newborns with ABO-HDN, 95 cases (13%) had blood group A and 84 cases (11.5%) had blood group B. No significant relationship was found between A and B blood groups in the newborns with the occurrence of ABO-HDN ( $p=0.1$ ). There was a significant difference between neonates with ABO and those without ABO in terms of bilirubin ( $p= 0.001$ ), hemoglobin ( $p=0.003$ ), and reticulocyte ( $p=0.036$ ) counts. A significant relationship between platelet count and the occurrence of ABO-HDN was not found ( $p= 0.558$ ).

**Conclusion:** The results showed that a large percentage of neonates are affected by ABO-HDN and provisions should be made to avoid possible complications.

**Keywords:** ABO-HDN, hemolytic anemia, neonatal blood parameters

### **Introduction**

The hemolytic disease of the newborn (HDN) is a type of anemia characterized by jaundice in newborns or infants. HDN, depending on the severity of the disease, can have such complications or symptoms as hepatosplenomegaly, liver failure, ascites, stillbirth due to heart failure, and brain damage (1-3). Etiologically, HDN can occur due to either immune or non-immune causes. Non-immune causes include: 1. Acquired defects in red blood cells caused by Cytomegalovirus (CMV)

infection, toxoplasmosis, syphilis, and some types of bacteria or disseminated intravascular coagulation (DIC), 2. Congenital defects of red blood cells such as membrane and enzyme disorders, 3. Hemoglobinopathies. Glucose-6-phosphate dehydrogenase (G6PD) deficiency and hereditary spherocytosis are the most important non-immune causes of HDN (4). Immune causes include incompatibility of different blood groups such as ABO and Rh, and congenital autoimmune diseases (5). In the ABO/Rh

incompatibility, maternal immune system identifies the fetal red blood cell antigens as foreign and makes antibodies against them. Such antibodies enter the fetus's body and attack the red blood cells and lyse them, culminating in anemia and neonatal jaundice, or even in extreme cases, fatal brain damage (6). The immune HDN is a clinical state during which the fetal red blood cells are destroyed by maternal IgG alloantibodies. During pregnancy, some fetal antigens pass through the placenta and enter the maternal blood stream (5-6).

Blood group incompatibility between the mother and fetus may be displayed in any of the following conditions: 1. The ABO blood group incompatibility that is the most common type, 2. Rh system incompatibility that is the most severe type, 3. Incompatibility of other blood group systems such as Kidd, Duffy, Kell, etc. (7-9). HDN caused by ABO incompatibility is often not severe because of three reasons: 1) Blood group antigens are not well developed early after birth, 2) The amount of these antigens is low during the fetal period, and 3) The antibodies against ABO antigens are often immunoglobulin M (IgM) which cannot pass the placenta (10, 11). HDN caused by ABO incompatibility is the leading cause of neonatal jaundice which may generate serious problems in the fetus or the newborn. If the mother has blood group O, this incompatibility can lead to more fulminant complications because the mother has IgG type Anti-AB. However, there have been few reports about mothers with A or B blood groups (12). The number of infants diagnosed with this condition each year is different in various societies and may vary from one in every 150 births to one in every 3,000 births (13). Therefore, this study was conducted in a small population in the Lorestan province of Iran. However, due to the clinical importance of HDN, careful examination on a large scale and the

investigation of the associated risk factors are required.

## **Materials and Methods**

The study was designed based on a cross-sectional approach. The medical records of babies born in the hospitals of Khorramabad, Iran, in 2014 and the first half of 2015 with anemia or jaundice were evaluated (765 cases). Some studies have mentioned that hyperbilirubinemia is the only ABO-HDN laboratory finding. Hemoglobin level is often normal but it can be about 10-12 gr/dl (3, 14). These babies had been hospitalized because of suspected HDN. Generally, normal hemoglobin for a newborn infant ranges from 14.6 to 20.4; hence, neonates (mature or premature) with hemoglobin levels of less than 14 who also displayed clinical symptoms were considered anemic. Additionally, jaundice is considered pathologic if it presents within the first 24 hours after birth. If the serum bilirubin level was  $> 13.9$  mg/dl in neonates and  $> 15$  mg/dl in premature infants or  $> 5$  mg/dl in the first day of life,  $> 10$  mg/dl in the second day, and  $> 15$  mg/dl in the third day, the diagnosis of pathological jaundice (based on clinical signs and birth weight) would be definitive (15). The criterion for the selection of newborns was anemia or an increase in bilirubin levels. Therefore, neonates with both elevated hemoglobin values greater than 14 and high bilirubin levels were also included in the study.

“Full-term infant” was defined as being born at a gestational age of 37-42 weeks and “premature infant” was defined as being born at a gestational age of less than 37 weeks. If maternal blood group was O and the baby’s blood group was A or B, or if maternal blood group was A, and the baby’s was B (or vice versa), the possibility of developing ABO-HDN was considered. After determining HDN, its cause (whether immune or non-immune) was determined by the evaluation of the blood group, Coombs test results, G6PD

level, or having a history of hereditary spherocytosis.

Furthermore, information such as maturity, prematurity, gender, hemoglobin levels, serum bilirubin levels, reticulocyte count and candidacy for blood transfusions were also assessed in newborns. The red blood cells and platelets, bilirubin, and reticulocytes were measured by Sysmex KX-21N (Japan) cell counter, Hitachi 902 Autoanalyzer (Japan), and manually, respectively. Infants who had undergone phototherapy prior to the study were excluded.

### **Statistical analysis**

After collecting the data and entering them into the SPSS, central tendency and dispersion were calculated. The chi-squared test, independent t-test, and the Mann-Whitney test were used for data analysis and the results were reported at 5% significance level. Moreover, the phi coefficient or Cramer's V were used to measure the degree of association between qualitative variables.

## **Results**

Out of 765 newborns, 78 cases (10.2%) had non-immune HDN, 29 cases (3.8%) had Rh-HDN, and 186 cases (24.3%) had ABO-HDN; hence, in total 293 cases (38.3%) had immune and non-immune HDN and 186 cases (24.3%) had ABO-HDN. The relationship between several parameters and the occurrence of HDN was analyzed (Table I).

The analysis showed that 3 cases (0.4%) of blood transfusions occurred in patients with ABO-HDN. However, there was no significant relationship between the number of blood transfusions and the occurrence of ABO-HDN ( $p = 0.775$ ). The relationship between the exchange transfusion rate and non-immune HDN was also examined. Blood transfusions were performed in 6 cases (0.8%) for patients with non-immune HDN, and there was a significant relationship between blood transfusions and non-immune HDN

( $p = 0.005$ ). The correlation between the two variables was 0.13, which shows a weak association between the two variables.

The relationship between the ABO-HDN and blood group, maternal blood group, preterm birth, and the gender of the newborns was also analyzed. The number of patients with ABO-HDN among neonates born with blood group A was 95 (13%) and in neonates born with blood group B was 84 cases (11.5%). There were no significant relationships between neonatal blood group A and B with the occurrence of ABO-HDN ( $p=0.1$ ). Thirteen mothers (2.7%) with blood group A, 12 mothers (2.5%) with blood group B, and 147 mothers (30.4%) with blood group O had newborn babies with ABO-HDN. Because mothers with the AB blood group do not have Anti-A or Anti-B antibodies, they were excluded from the study. Based on the chi-squared test, there was a significant relationship between maternal blood group and the occurrence of ABO-HDN ( $p < 0.001$ ). The degree of association between the two variables is 0.45 as calculated by the phi coefficient, which shows a moderate association between the two variables. The analysis conducted to find the relationship between preterm birth and ABO-HDN showed that the number of premature neonates was 16 (2.2%) among patients with ABO-HDN and the chi-squared test showed a significant relationship between birth age and the occurrence of ABO-HDN ( $p = 0.004$ ). The degree of association between the two variables was obtained as -0.1 using the phi coefficient, which indicates a very weak relationship between the two variables. The relationship between the occurrence of ABO-HDN and gender was also studied. The number of female newborns with ABO-HDN was 78 (10.2%), the number of male newborns among patients with ABO-HDN was 108 (14.1%). There was no significant relationship between gender and the

occurrence of ABO-HDN ( $p = 0.797$ ) (Table II).

The analysis of the relationship between preterm birth and non-immune HDN indicated that the number of premature newborns among infants with non-immune HDN was 4 (0.5%). There was a significant relationship between birth age and non-immune HDN ( $p = 0.005$ ). The degree of association between the two variables was calculated as -0.1 using the phi coefficient, which suggests the presence of a very weak association between the two variables.

The relationship between the occurrence of non-immune hemolytic disease and gender was studied. The number of female non-immune HDN patients was 13 (1.7%) and that of male patients was 65 (8.5%). There was a significant relationship between the occurrence of non-immune HDN and gender ( $p < 0.001$ ). The phi coefficient was used to measure the degree of association between the two variables as -0.16, which is indicative of a very weak inverse association between the two variables (Table III).

The mean total bilirubin level in newborns with ABO-HDN was  $15.292 \pm 3.11$  and, in newborns without ABO-HDN, it was  $14.216 \pm 3.91$ . There was a significant difference in total bilirubin levels between the two groups ( $p < 0.001$ ). On the other hand, the average direct bilirubin level in newborns with ABO-HDN was  $0.760 \pm 0.19$  and in newborns without ABO-HDN was  $0.733 \pm 0.26$ . There was no significant difference between the two groups in terms of direct bilirubin levels ( $p = 0.072$ ).

The average total bilirubin level in newborns with non-immune HDN was  $15.784 \pm 3.9$  and for newborns without non-immune HDN, this figure was  $14.332 \pm 3.7$ . There was a significant difference in total bilirubin levels between the two groups ( $p = 0.001$ ). Furthermore, the average direct bilirubin level in newborns with non-immune HDN was  $0.819 \pm 0.35$  and for newborns without non-immune HDN, it was  $0.730 \pm 0.22$ . There was a

significant difference between the direct bilirubin levels of the two groups ( $p = 0.005$ ).

The mean age of the mothers of newborns with ABO-HDN was  $29.8 \pm 5.844$  years and that of newborns without ABO-HDN was  $29.35 \pm 5.59$  years. The two groups showed no significant difference in maternal age ( $p = 0.350$ ). The average age of the mothers of newborns with non-immune HDN was  $29.18 \pm 5.474$  and in newborns without non-immune HDN, it was  $29.49 \pm 5.681$ . There was no significant difference in maternal age between the two groups (0.655).

The mean hemoglobin level in newborns with and without ABO-HDN was  $14.917 \pm 2.32$  and  $15.438 \pm 2.69$ , respectively. There was a significant difference in the two groups ( $p = 0.018$ ).

The mean hemoglobin level in newborns with non-immune HDN was  $14.458 \pm 2.7994$  and in newborns without non-immune HDN, it was  $15.406 \pm 2.5781$ . There was a significant difference between the two groups in terms of hemoglobin levels ( $p = 0.003$ ).

The average platelet count in newborns with ABO-HDN was  $302.853 \pm 100.99$  and in newborns without ABO-HDN, it was  $295.873 \pm 99.87$ . There was no significant difference in the platelet count between the two groups ( $p = 0.412$ ). The average platelet count in newborns with non-immune HDN was  $291.19 \pm 106.76$  and in newborns without non-immune HDN was  $298.30 \pm 99.44$ . There was no significant difference in the platelet count between the two groups ( $p = 0.558$ ).

The average reticulocyte count in newborns with ABO-HDN was  $1.761 \pm 1.64$  and, it was  $1.498 \pm 1.69$  in newborns without ABO-HDN. There was a significant difference in reticulocyte count between the two groups ( $p = 0.036$ ). The average reticulocyte count in newborns with non-immune HDN was  $1.636 \pm 1.68$  and, in newborns without non-immune HDN, it was  $1.55 \pm 1.68$ . There was no

significant difference in the reticulocyte count between the two groups ( $p = 0.708$ ). The mean age of the newborns with ABO-HDN at admission was  $5.64 \pm 3.77$  days and in newborns without ABO-HDN, it was  $6.31 \pm 4.70$  days. There was no significant difference between the mean ages of the two groups at admission ( $p=0.215$ ) (Table IV). In addition, the value of this variable was  $6.17 \pm 4.44$  days in newborns with non-immune HDN and  $6.15 \pm 4.511$  in newborns without non-

immune HDN. There was no significant difference between the two groups in terms of the age of the newborns at admission ( $p = 0.971$ ) (Tables IV and V). Among the 765 infants studied, 686 participants (90%) had normal G6PD activity. G6PD enzyme levels in 78 newborns (0.10%) with non-immune HDN were reduced and there was a significant relationship between G6PD level and the occurrence of non-immune HDN ( $p < 0.001$ ).

*Table I: The contingency table of neonates suffering from anemia and jaundice in terms of having received blood transfusions and developing ABO-HDN and non-immune HDN*

		blood transfusions			P-value
		done	Not done		
Non-immune hemolytic disease (%)	posses	6(0. 8)	72(9. 4)	0.005	
	lack	11(1. 4)	676(88. 4)		
ABO-HDN (%)		posses	3(0. 4)	183(23. 9)	0. 775
		lack	14(1. 8)	565(73. 9)	

Table II: The contingency table of neonates with anemia and jaundice in terms of blood group, maternal blood group, maturity, gender, and the occurrence of ABO-HDN

		ABO-HDN		P-value
		posses		
		A	95(13)	168(23)
Newborn blood group (%)	A			0.001>
	B	84(11. 5)	106(14. 5)	
	O	0(0)	248(33. 9)	
	AB	7(1)	24(3. 3)	
Maternal blood group(%)	A	13(2. 7)	127(26. 3)	
	B	12(2. 5)	68(14. 1)	<0. 001
	O	147(30. 4)	116(24)	
	mature	167(22. 5)	463(62. 3)	
Birth age (%)	premature	16(2. 2)	97(13. 1)	0.004
	female	78(10. 2)	236(30. 8)	
Newborn gender(%)	male	108(14. 1)	343(44. 8)	0. 797

Table III: The contingency table of newborns with anemia and jaundice in terms of gender, maturity and prematurity, and the occurrence of non-immune Hemolytic disease

		non-immune Hemolytic disease		P-value
Birth age (%)	mature	posses	lack	
	premature	(14. 7) 109	4(0. 5)	
Newborn gender (%)	female	301(39. 3)	13(1. 7)	<0. 001
	male	386(50. 5)	65(8. 5)	

Table IV: The comparison of bilirubin levels, reticulocytes, hemoglobin, platelets, maternal age, and birth age in patients with or without ABO-HDN

Quantitative variables	ABO-HDN				P-value
	posses		lack		
	Numbers	Mean ± SD (Median)	Number	Mean ± SD (Median)	
<b>Maternal age (year)</b>	181	29. 80±5. 844 (30)	559	29. 35±5. 596 (29)	0. 350
<b>Indirect T Bilirubin(mg/dl)</b>	186	15. 292±3. 1140 (15. 15)	573	14. 216±3. 9196 (14. 2)	<0. 001
<b>Bilirubin D(mg/dl)</b>	154	0. 760±0. 1985 (0. 8)	494	0. 733±0. 2602 (0. 7)	0. 072
<b>Hemoglobin (gram/dl)</b>	186	14. 917±2. 3293 (15. 05)	571	15. 438±2. 6914 (15. 6)	0. 018
<b>Platelets(×10<sup>9</sup>/liter)</b>	184	302. 853±100. 9945 (283)	565	295. 873±99. 8799 (285)	0. 412
<b>Reticulocytes(%)</b>	174	1. 761±1. 6457 (1. 1)	537	1. 6953±1. 498 (1)	0. 036
<b>The newborns' age(day)</b>	186	5. 64±3. 770 (5)	579	6. 31±4. 704 (5)	0. 215

Table V: The comparison of bilirubin levels, reticulocyte count, hemoglobin levels, platelets, and maternal and birth age in newborns with and without non-immune hemolytic disease

Quantitative variables	Non-immune hemolytic disease				P-value	
	posses		lack			
	numbers	Mean ± SD (Median)	numbers	Mean ± SD (Median)		
<b>Maternal age (year)</b>	76	29. 18±5. 474 (29)	664	29. 49±5. 681 (30)	0. 655	
<b>Indirect T Bilirubin(mg/dl)</b>	77	15. 784±3. 9031 (14. 7)	682	14. 332±3. 7233 (14. 4)	0. 001	
<b>Bilirubin D(mg/dl)</b>	69	0. 819±0. 3566 (0. 8)	579	0. 730±0. 2292 (0. 7)	0. 005	
<b>Hemoglobin (gram/dl)</b>	77	14. 458±2. 7994 (14. 8)	680	15. 406±2. 5781 (15. 6)	0. 003	
<b>Platelets(×10<sup>9</sup>/liter)</b>	76	291. 197±106. 7669 (277)	673	298. 309±99. 4136 (285)	0. 558	
<b>Reticulocytes(%)</b>	67	1. 6831±1. 636 (1)	644	1. 6874±1. 555 (1)	0. 708	
<b>The newborns' age(day)</b>	78	6. 17±4. 444 (5)	687	6. 15±4. 511 (5)	0. 971	

## Discussion

In the present study, the rate of HDN in infants hospitalized with anemia or jaundice was 38.3%. Other similar studies have reported the general prevalence of HDN to be between 31% and 35% (16, 17). In a study performed in Lady Reading Hospital of Pakistan, 200 infants (70% male and 30%) were selected. Most of the infants (99.5%) were between 0-10 days and only 0.5% were 13 days old or older. Among these 200 infants, ABO and Rh incompatibility in infants with jaundice were reported as 22.5% and 12.5%, respectively. In the remaining 65%, physiologic jaundice was diagnosed in 40.5% of the infants, prematurity was

identified in 15%, and G6PD was detected in 9.5% of the infants. In 22.5% of ABO incompatibility cases, 16.5% were male and 6% were female (16). Additionally, in the present study, the prevalence rates of immune and non-immune HDN were 28.1% and 10.2%, respectively. Among the immune HDNs, the prevalence of ABO-HDN was 24.3%, which is consistent with other studies (12, 18). In general, some studies have estimated the prevalence of ABO-HDN to be 4.54 in every 1000 births (19). ABO-HDN is usually not so severe that the patient requires blood transfusions (20, 21). It should be noted that the severity of hemolysis in the fetus in blood

incompatibilities such as Kell and Rh blood group incompatibilities is so high that it is likely that the patient will require blood transfusions both before and after birth (22, 23). In the present study, only three infants with ABO-HDN were encountered that needed blood transfusions, whereas, infants suffering from non-immune HDN required blood transfusions significantly more than the ABO-HDN group.

In the present study, the number of infants with ABO-HDN who received blood transfusions was 3 (0.4%) and there was no significant relationship between blood transfusion and ABO-HDN.

The relationship between ABO-HDN and blood group, maternal blood group, preterm birth and the gender of the newborns were also analyzed in the present study.

Although infants born from mothers with blood group O were at the highest risk for developing HDN, their own blood group did not play a significant role in this matter, and no significant relationship was observed between blood groups A and B with the likelihood of developing ABO-HDN ( $p = 0.1$ ). In a similar study that examined 151 infants in India, no relationship was found between O-A and O-B blood groups with the occurrence of hemolytic diseases in the infants (24).

In the present study, it also became clear that there is no significant relationship between gender and the likelihood of occurrence of ABO-HDN ( $p = 0.797$ ). However, there was a significant relationship between the occurrence of ABO-HDN and the maturity/prematurity of the newborns, the prevalence being higher in mature babies ( $p = 0.005$ ).

Total bilirubin levels in newborns with ABO-HDN was significantly higher ( $p < 0.001$ ). Many studies have pointed this fact out (25-29). No significant relationship was found between maternal age and the occurrence of any form of HDN. The mean hemoglobin level in infants hospitalized with ABO-HDN was  $2.32 \pm$

$14.92$ . This value was significantly different from the hemoglobin levels of neonates without ABO-HDN ( $2.69 \pm 15.44$ ).

However, there were no significant relationships between the platelet counts of infants with any form of HDN and infants not suffering from HDN.

Reticulocyte count was different between infants with immune and non-immune HDN, such that in infants with non-immune HDN, the platelet count was not significantly different from that of neonates without HDN, whereas, neonates with ABO-HDN showed a significant increase in platelet count in comparison with other neonates ( $p = 0.036$ ).

Akgul et al., studied the effect of the infant's blood group on the severity of hemolysis and jaundice caused by ABO incompatibility. In a prospective analysis of 166 patients with ABO-HDN, risk factors affecting jaundice severity in infants with blood groups A and B were assessed. Both groups had similar demographic characteristics such as birth weight, sex, and hospital stay duration. There was no statistically significant difference in hematologic parameters, including the first hemoglobin level, the first and last indirect bilirubin levels, frequency of positive direct Coombs test results, hemolytic findings in peripheral blood smear, phototherapy duration, the number of blood transfusions received, and IVIg treatment. The authors concluded that the severity of hemolytic jaundice in ABO incompatibility is not affected by blood group at all (26).

In a study by Gilja et al., conducted in 1988, it was shown that there is no need to treat blood incompatibility in most cases of neonatal ABO-HDN. Severe hemolysis cases that required blood transfusions were less common and hydrops fetalis was rare (30). Given the fact that there was a significant relationship between hemoglobin levels and total bilirubin levels in neonates suffering from ABO-HDN, it is necessary that measures be

taken regarding the birth of neonates with the A or B blood groups born from mothers with the blood group O, because it is likely that bilirubin levels will increase day by day after birth and reach dangerous levels in these infants.

It is recommended that similar studies be conducted on larger scales in our country, especially with regard to other blood group incompatibilities. These findings were consistent with other studies showing that the high rate of hemolytic anemia in infants is caused by ABO blood type incompatibilities.

## Conclusion

In conclusion, VPA induced apoptosis and The results showed that a large percentage of neonates are affected by ABO-HDN and provisions should be made to avoid possible complications.

## Conflict of interest

The authors report no conflict of interest.

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