

## **Outcome of Jaundice in neonates with ABO and Rh blood incompatibility and glucose-6-phosphate dehydrogenase deficiency.**

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### **Abstract**

**Background:** Neonatal jaundice is the most common complaint in the early days of birth that can potentially results in important and irreversible effects. The aim of this study was to evaluate the severity and outcome of jaundice in newborns with ABO and Rhesus (Rh) incompatibility and glucose-6-phosphate dehydrogenase (G6PD) deficiency.

**Methods:** Data of this cross-sectional study was collected using medical records of neonates with diagnosis of jaundice, admitted in the neonatal ward of Abuzar Teaching Hospital, located in Ahvaz, Southwest Iran.

**Results:** Out of 1119 neonates, 272 (24.3%), 11 (1%), and 112 (10%) had ABO incompatibility, Rh incompatibility, and G6PD deficiency respectively. There was no significant difference in neonates with ABO or Rh incompatibility, and G6PD deficiency with severe hyperbilirubinemia ( $P=0.04$ ). A patient with ABO incompatibility and two neonates with Rh incompatibility and five neonates with G6PD deficiency were suffering the dire consequences of neonatal jaundice (Kernicterus) that the Catching rate in the last two groups was significantly more than other neonates.

**Conclusion:** the occurrence of jaundice in neonates with Rh incompatibility and G6PD deficiency is with dire outcomes than other neonates.

**Keywords:** Jaundice, Neonatal, Rh-Hr blood-group system, ABO blood-group system, Blood group incompatibility, Glucosephosphate dehydrogenase deficiency, Outcomes.

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### **Introduction**

Neonatal jaundice is one of the most common concerns that lead to go parents to the infant health centers. While the majority of these cases does not have significant clinical importance but their difference with pathological jaundice has very importance. For example, high bilirubin at birth can be important and has irreversible effects on the nervous system (Kernicterus) that this characterizes a matter of high importance to treat neonatal jaundice [1]. Pathological jaundice has very diverse causes that one of its important causes is hemolytic ones (ABO or Rh incompatibility) as well as glucose 6 phosphate dehydrogenase (G6PD) deficiency. Among all these causes, ABO incompatibility is more common. ABO incompatibility can be occurred following any pregnancy in the mothers with blood group O, after sensitivity to fetal erythrocytes. Several studies have introduced ABO incompatibility as the most common risk factor in the premature pathological jaundice [2-4]. Another cause, but relatively rare, of pathological neonatal jaundice is Rh incompatibility. The prevalence of Rh D isoimmunization has reduced due to create a method for prevention of

isoimmunization of mothers with Rh antigens. Rh incompatibility is considered an important cause of neonatal jaundice. The outcome of this disease includes haemolysis, hydrops, and the death of fetus or newborn (in severe cases and no medical intervention) [5,6]. G6PD deficiency is another factor for neonatal jaundice. It is the most common enzymatic disorder in the man with about 400 million patients. In addition to attacks of acute hemolysis, this disease can manifests with severe jaundice [7]. Several studies have been conducted on jaundice in Iran, but unfortunately there is no investigation regarding the severity and outcome of neonatal jaundice in newborns with ABO and Rh incompatibility, and G6PD deficiency. This study aimed to answer to this question.

### **Methods**

This cross-sectional study was conducted in the neonatal ward of Abuzar Teaching Hospital, located in Ahvaz, Southwest Iran. Medical records of all neonates hospitalized due to jaundice were evaluated from April 2010 to September 2011. The study was approved by Ethical Committee of Ahvaz Jundishapur University of Medical Sciences (Ref. No. IA/P/

8/20/2250). If the neonates had been hospitalized several times, first time of hospitalization were studied. Finally, out of 1233 neonates' medical document, 1119 of them were studied. Criteria for inclusion were all neonates with the diagnosis of jaundice as well as G6PD tests and blood group and Rh testing of mother and newborn. The exclusion criteria were the incomplete files and neonates with G6PD deficiency and ABO or Rh incompatibility concurrently. After the study was approved by the Ethical Committee of Ahvaz Jundishapur University of Medical Sciences as well as getting informed consent from parents, the data were collected by a researcher using a checklist. The recorded data included gender, total and direct bilirubin, hemoglobin and hematocrit, maternal and neonatal blood group and Rh, reticulocyte rate, direct Coombs, and G6PD testing.

Neonates with blood group A or B of mothers with blood group O were considered as ABO incompatibility. Moreover, newborns with a positive Rh born from mothers with a negative Rh were defined as Rh incompatibility [5]. The clinical status of the patient during hospitalization and discharge were recorded through data in the neonatal file. Based on discharge status, the neonates were divided into three categories: the first category was infants discharged with the good general condition; the second category was infants discharged with complications resulting from hyperbilirubinemia (Kernicterus); the third category: infants who died due to jaundice. Kernicterus can be divided into acute and chronic bilirubin encephalopathy. Acute bilirubin encephalopathy (ABE) consists of decreased feeding, lethargy, variable abnormal tone (hypotonia and/or hypertonia), high-pitched cry, retrocollis and opisthotonus, setting sun sign, fever, seizures, and death [8]. Based on laboratory results of total bilirubin, hyperbilirubinemia was divided into two severe (over 25) and non-severe categories (equal or under 25) [9]. Student's t-test, Fisher's test, and Chi square were used for analyzing the data. Significance level was considered 0.001. Data were analyzed using SPSS 19.

## Results

Out of 1233 neonates with diagnosis of jaundice, 1119 neonates had inclusion criteria in this study. A total of 16 neonates concurrently with G6PD deficiency and ABO or Rh incompatibility were excluded. Of this number, 636 (56.8%) were boy and 483 (43.2%) were girls. In total, out of 283 (25.3%) neonates with ABO or Rh incompatibility, 11 cases (1%) had Rh incompatibility and 272 cases (24.3%) had ABO incompatibility. A total of 112 cases (10%) were also diagnosed with G6PD deficiency. Out of 283 newborns with blood incompatibility, 140 cases (49.6%) were male and 143 (50.4%) were female. There was no significant difference between gender and blood incompatibility ( $P=0.05$ ). Of 112 infants with G6PD deficiency, 89 (79.5%) were male and 23 (20.5%) were female. According to our study, G6PD deficiency in boys significantly was more than girls ( $P=0.007$ ).

According to Table 1, no significant statistical difference was seen in total bilirubin, direct bilirubin, hemoglobin, hematocrit,

and reticulocyte count between two groups of newborns with ABO and Rh incompatibility or neonates with G6PD deficiency. The frequency of severe hyperbilirubinemia in various causes has been shown in Table 2. In addition, the percentage of incidence of kernicterus among the same group is also shown. No significant difference was observed between neonates suffering from ABO or Rh incompatibility neonates with G6PD deficiency in the severity of hyperbilirubinemia ( $P=0.04$ ). Table 3 shows a comparison between newborns with Rh or ABO blood incompatibility, and or with G6PD deficiency, with infants who were not part of either group in the outcome of jaundice. Out of all neonates hospitalized due to jaundice, 1107 (98.8%) with good public mood were discharged; on the other hand, 12 neonates (1.2%) demonstrated Kernicterus. Among neonates with Kernicterus, 7 neonates (0.7%) died, and 5 neonates (0.5%) were discharged with brain-neurologic signs of Kernicterus.

**Table 1.** Comparison of hematologic data in infants with ABO and Rh incompatibility with G6PD deficiency neonates.

| Laboratory findings        | Neonates with blood incompatibility | Neonates with G6PD deficiency | P-value |
|----------------------------|-------------------------------------|-------------------------------|---------|
| Mean total bilirubin mg/dl | 20.31 ± 4.08                        | 20.17 ± 4.07                  | 0.3     |
| Mean direct bilirubinmg/dl | 0.6 ± 0.4                           | 0.68 ± 0.7                    | 0.15    |
| Hemoglobin gr/dl           | 15.01 ± 2.6                         | 15.9 ± 2.3                    | 0.23    |
| Hematocrit (percentage)    | 42.7 ± 7.3                          | 43.7 ± 9.3                    | 0.5     |
| Reticulocytecount          | 1.51 ± 2.03                         | 1.04 ± 1.48                   | 0.1     |

In fact, Kernicterus was the cause of death in all cases. According to Table 3, out of 11 neonates with Rh incompatibility, 2 neonates (18.2%) had Kernicterus and then died while out of 272 infants with ABO compatibility, one patient (0.4%) suffered Kernicterus and was discharged with neurological signs. Out of all new-borns with G6PD deficiency, 5 new-borns (4.5%) suffered Kernicterus, which two new-borns (1.8%) died.

Kernicterus in neonates with G6PD deficiency was significantly higher than ABO incompatibility ( $P=0.03$ ). Also, no statistical difference in the deaths caused by Kernicterus was seen between neonates with ABO or Rh incompatibility with neonates with G6PD deficiency (Table 3).

## Discussion

Various studies show large differences in the prevalence of neonatal jaundice in the world. This difference is more pronounced, especially for G6PD deficiency [10,11]. In the present study, 25.3% of neonates had ABO or Rh incompatibility and 10% were with G6PD deficiency. In study conducted by Rasul et al. in Bangladesh, ABO or Rh incompatibility were 16.7% of all causes of neonatal jaundice [10]. Rahim et al. in Pakistan showed that 26.6% of icteric

newborns had G6PD deficiency [11]. Since G6PD deficiency is a recessive X disease, it is expected that occurrence of this disease in males would be greater than females [12]. In our study also the ratio of boys to girls in neonates with G6PD deficiency was about 3.9/1 (P<0.001). In a study by Abolghasemi et al. [13], this ratio was 6/1. In a study by Rahim et al. [14], this ratio in infants with normal G6PD was 3.63/1 and in neonates with G6PD deficiency was 7/1. In a study

conducted by Eghbalian and Monsef about G6PD deficiency in icteric newborns without hemolysis, the ratio of boy to girl was 5/1 [15]. In all the mentioned studies, significant difference observed between the rate of G6PD deficiency in boys and girls [16]. This difference also probably arises from the different sample size of the studies as well as racial and genetic differences.

**Table 2.** The frequency of neonates hospitalized due to non-severe hyperbilirubinemia (Total bilirubin under 25 mg/dl) and severe hyperbilirubinemia (Total bilirubin equal to above 25 mg/dl).

| Type of Disease     | Severe Hyperbilirubinemia |   | Non-severe Hyperbilirubinemia |   |
|---------------------|---------------------------|---|-------------------------------|---|
|                     | Frequency (all subjects)  | Percentage of catching in people the same group | Frequency (all subjects)      | Percentage of catching in people the same group |
| ABO incompatibility | 31 (28.7%)                | 0.114   | 241 (23.8%)                   | 0.886   |
| Rh incompatibility  | 5 (4.6%)                  | 0.455   | 6 (0.6%)                      | 0.545   |
| G6PD                | 17 (15.7%)                | 0.152   | 95 (9.4%)                     | 0.848   |
| Other neonates      | 55 (49.1%)                | 0.082   | 669 (66.2%)                   | 0.918   |
| Total               | 108 (9.7%)                | -   | 1011 (90.3%)                  | -   |

**Table 3.** Outcomes of jaundice in neonates with (ABO or Rh) blood incompatibility and neonates with G6PD deficiency and other infants.

|                  | Number                       | Infants with G6PD deficiency infants (n=112) | Infants with ABO or Rh deficiency (n=283) | Other infants (n=724) |
|------------------|------------------------------|--|---|-----------------------|
|                  |                              |  |   |                       |
| Public good mood | Number                       | 107  | 280                                       | 720                   |
|                  | Compared to all subjects (%) | 0.097  | 0.253                                     | 0.65                  |
|                  | Compared to group (%)        | 0.955  | 0.989                                     | 0.995                 |
| Kernicterus      | Number                       | 5  | 3   | 4                     |
|                  | Compared to all subjects (%) | 0.417  | 0.25                                      | 0.333                 |
|                  | Compared to group (%)        | 0.045  | 0.011                                     | 0.006                 |
| Death            | Number                       | 2  | 2   | 3                     |
|                  | Compared to all subjects (%) | 0.286  | 0.286                                     | 0.428                 |
|                  | Compared to group (%)        | 0.018  | 0.007                                     | 0.004                 |

In our study, severe hyperbilirubinemia in neonates with Rh incompatibility occurred more than neonates with ABO incompatibility (45.5% versus 11.4). This finding is similarly was confirmed by Weng and Chiu’s study [5]. In addition, Girish et al. showed that 66.6% of newborns with Rh incompatibility needed to exchange transfusion [17]. In other studies, also 60-90% of newborns with blood incompatibility were in need of exchange transfusion [3,18]. All of these studies have stressed unanimously on more severe hyperbilirubinemia in this group of neonates. According to the results of our study, neonatal hyperbilirubinemia was observed in 15.7% of neonates with G6PD deficiency. Also, 49.1% of neonates who were not part of any of the two groups suffered a severe hyperbilirubinemia. In the study Abolghasemi et al., almost 23.5% of neonates presented hyperbilirubinemia above 20 mg/dl [13]. Some studies have shown that half of neonates

with G6PD deficiency had remarkable hyperbilirubinemia [19]. Concerns of pediatricians about neonatal jaundice are due to potential risk of Kernicterus and morbidities and mortalities associated with it. Although the exact mechanism of this degradation is unknown, it has been attributed to the toxicity in the nervous system. These effects are associated with increasing of bilirubin while no immune border exist for serum bilirubin for catching level in order to ensure the absence of suffering the risks aroused by hyperbilirubinemia [5]. Most cases of kernicterus occur in neonatal with bilirubin more than 20 mg/dl that can be more likely to make this case in keeping with some underlying diseases such as G6PD deficiency and Rh incompatibility [20].

In our study the rate of Kernicterus in neonates with G6PD deficiency as well as Rh incompatibility was considerably higher than ABO incompatibility. These results are consistent

with the results of the study conducted by Weng and Chiu [5]. In the study conducted by Rasul et al., out of 426 neonates with hyperbilirubinemia, nine neonates had Kernicterus. Of these, two neonates were with ABO incompatibility (out of 48 neonates with ABO incompatibility) and four newborn were with Rh incompatibility (out of 23 neonates with Rh incompatibility). It represents the high frequency of Kernicterus in Rh incompatibility [8,17]. In a study, out of 61 cases (31.5%) with kernicterus 19 cases showed G6PD deficiency. Similar to our study, all of the above studies represent an increase in mortality and morbidity caused by jaundice in neonates with G6PD deficiency and Rh incompatibility.

### Limitations

This study was retrospective and only neonates were studied that laboratory findings had been recorded in their files. Additionally, according to perform some of experiments in other centers and the lack of record of their results in the neonates' file, some neonates did not obtain the inclusion criteria.

### Conclusion

Our findings showed that morbidity and mortality of jaundice in newborns with G6PD deficiency, and Rh incompatibility was more than its occurrence in newborns with ABO incompatibility; therefore, such neonates would need more care. According to high rate of neonatal jaundice complications in these neonates, screening of G6PD activity for diagnosis would be effective in reducing complications of neonatal jaundice.

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