J Compr Ped. 2021 November; 12(4):e109539. doi: 10.5812/compreped.109539.

Published online 2021 October 19. **Research Article**

Causes of Neonatal Jaundice Requiring Exchange Transfusion

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Received 2020 September 19; **Revised** 2021 August 03; **Accepted** 2021 August 16.

Abstract

Background: Neonatal jaundice is highly prevalent in Asia and has serious complications, such as kernicterus. Therefore, it is very important to identify the risk factors of jaundice requiring exchange transfusion since it can be helpful in the prevention of the disease and early diagnosis of its complications.
Objectives: The present study aimed to identify the causes of neonatal jaundice requiring blood exchange.
Methods: The present cross-sectional study was performed on 251 term and preterm neonates. The studied newborns were 2-14 days old (born at $\geq$ 35 weeks of gestation) with jaundice and bilirubin of more than 17 mg/dL and received exchange transfusion during 2011 - 2020 in Ghaem teaching hospital, Mashhad, Iran. The required data of the study variables, such as hyperbilirubinemia risk factors, laboratory tests, the documented history of the mothers and neonates, and physical examination results, were collected through a questionnaire and the medical records of the patients. Finally, the collected data were analyzed in SPSS software (version 20).
Results: Based on the results, the mean value of the total serum bilirubin level in neonates who received exchange transfusion was 27.53 $\pm$ 10.05 mg/dL. The blood types of about 40% of mothers and their neonates were O and A/B, respectively. Moreover, 11.4% of mothers were Rh-negative; however, their neonates were Rh-positive. The results also revealed that the causes of exchange transfusion were unknown, ABO incompatibility, Rh incompatibility, glucose-6-phosphate dehydrogenase deficiency (G6PDD), and sepsis in 52.7 %, 24%, 7.1%, 5.3%, and 5.3% of the neonates, respectively.
Conclusions: The findings of this study suggest that after unknown causes, the most common causes of exchange transfusion were ABO incompatibility, Rh incompatibility, G6PDD, and sepsis. Therefore, since most of these causes can be recognized, it is recommended to perform related tests and take related measures in the Midwifery Department of the hospital to prevent the occurrence and exacerbation of jaundice. Moreover, it is recommended to perform an early follow-up after the discharge.

Keywords: Exchange Transfusion, Jaundice, Hyperbilirubinemia

1. Background

Hyperbilirubinemia, which is a common manifestation in neonates (1, 2), is in most cases physiological and does not require any special treatment. However, it is the most common cause of rehospitalization in early infancy. Based on statistics, 0.36 - 0.5% of term neonates, who are discharged from the hospital, are rehospitalized due to moderate to severe hyperbilirubinemia (3). However, only a few newborns with hyperbilirubinemia have a recognizable pathological underlying problem (1).

Identifying the causes of jaundice and appropriate measures can prevent dangerous jaundice. The early detection of Rh incompatibility in recent decades has led to the rapid diagnosis, prevention, and control of jaundice. The most common causes of hyperbilirubinemia are idiopathic jaundice, ABO incompatibility, Rh incompatibility, glucose-6-phosphate dehydrogenase deficiency (G6PDD), and sepsis (4, 5).

As an effective treatment for hyperbilirubinemia, phototherapy dramatically reduces the need for exchange transfusion (6, 7). Exchange transfusion is the replacement of all or most of the red blood cell mass and plasma volume of a recipient with those of one or more donors. In newborns with jaundice, blood exchange is performed when phototherapy fails to reduce the level of bilirubin in the blood, the risk of kernicterus is higher than the risk of this treatment, or the neonate has the symptoms of kernicterus (8, 9).

Given the high prevalence of neonatal jaundice in Asian countries, including Iran, its major complications (eg, kernicterus), and its multiple risk factors, the iden-

tification of the factors leading to jaundice requiring exchange transfusion can help the prevention of this disease and early diagnosis. Bilirubin intoxication is still one of the major health problems in neonates in countries with early hospital discharge. The first step before the early diagnosis and treatment of this disease is its prevention, requiring the identification of its risk factors. However, the identification of the risk factors of jaundice in newborns is still a serious issue and plays an important role in controlling jaundice and its primary causes.

Although there are numerous studies on the causes of neonatal jaundice risk factors, only few studies have probed into the causes of jaundice requiring blood exchange, most of which are small in sample size and fail to show less common causes. Therefore, this study examined this important issue in the Iranian community with a sample size of more than 200 term and preterm neonates, which is almost unique in terms of sample size.

2. Methods

The present descriptive cross-sectional study was performed on 251 newborns born at > 35 weeks of gestation, with jaundice, 2 - 14 days of age, bilirubin of > 17 mg/dL, and receiving exchange transfusions during 2011 - 2020 in Ghaem hospital, Mashhad, Iran. This study was approved by the Ethics Committee of Mashhad University of Medical Sciences with the project no. of 970391 and code of IR.MUMS.MEDICAL.REC.1397.466.

The subjects were selected using nonprobability and purposive sampling methods. The method for the determination of the sample size was adopted from a study conducted by Mokhtari et al. (10) on the causes of exchange transfusion. Accordingly, based on the following formula and considering the mean of the minimum and maximum prevalence, the sample size was calculated to be 250 subjects. Alpha and beta errors were considered 0.05 and 0.2, respectively.

$$n = \frac{Z^2 Pq}{D^2}$$

First, the list of the neonates who received exchange transfusion during the previously mentioned period was collected from the hospital archive. Subsequently, the term and preterm neonates who needed exchange transfusion were selected using the convenience sampling method. The inclusion criterion was icteric neonates with a gestational age of more than 35 weeks receiving transfusion exchange in Qaem hospital. The exclusion criteria were congenital anomalies, sepsis, and no availability of patients' test results and data.

The checklist forms were completed based on the neonatal examination, patient history, test results, and maternal and neonatal status (ie, age, gender, and major complaint). Moreover, the test results, which were required by the treating physician, were recorded by the researchers. Finally, by reviewing the patient status and examination and test results, the researchers started to study the causes of jaundice.

A patient was diagnosed with ABO incompatibility if the blood type of the mother was O+ and that of the neonate was A or B, and at least two of several conditions, including (1) jaundice on the first day, (2) neonate's positive direct Coombs' test, (3) microspherocytes in peripheral blood, and (4) positive indirect Coombs' test, were observed. If no Rh or ABO incompatibilities were observed, while the direct Coombs' test was positive in neonates, the result was considered sub-blood group incompatibility.

The samples were collected in tubes with ethylenediaminetetraacetic acid anticoagulant to be screened for G6PDD by the fluorescent spot test. This test is a qualitative method of screening that indicates the activity of the enzyme as sufficient or insufficient. Less than 30% of enzyme activity is usually reported to be insufficient (10). Finally, the information of all the patients was entered into SPSS software (version 20).

The Kolmogorov-Smirnov test was used to examine the distribution of weight, referral age, total bilirubin, and hematocrit. Hematocrit had a normal distribution; nevertheless, other variables did not have a normal distribution. Afterward, the descriptive statistics indicators, including central tendency and measures of variability, were calculated. In all the tests, a p-value of less than 0.05 was considered statistically significant.

3. Results

This study was initially conducted on a total of 272 neonates receiving exchange transfusion. However, 18 newborns were excluded due to having a gestational age under 34 weeks, and 3 more newborns were excluded since they received exchange transfusion for reasons other than jaundice. The remaining 251 cases were included in this study. The mean value of the total serum bilirubin level in neonates receiving exchange transfusion was 27.53 $\pm$ 10.05 mg/dL. According to the collected data, 85 (34.7%), 63 (25.7%), 47 (19.2%), 19 (7.8%), 14 (5.7%), 12 (4.9%), 4 (1.6%), and 1 (0.4%) neonates had A+, B+, O+, AB+, A-, B-, O-, and AB- blood types, respectively.

Regarding neonatal and maternal blood group set-up, 75 (38.9%), 46 (23.8%), 41 (21.2%), 22 (11.9%), and 9 (4.7%) subjects had ABO set-up, similar set-ups, set-ups of other

blood types, Rh set-up, and ABO and Rh set-ups, respectively. Regarding the causes of jaundice, 149 (52.7%), 68 (24%), 20 (7.1%), 16 (5.7%), 15 (5.3%), 2 (0.7%), 3 (1.1%), 1 (0.4%), 1 (0.4%), 1 (0.4%), 5 (1.8%), and 2 (0.7%) participants were afflicted with this disease due to unknown causes, ABO incompatibility, Rh incompatibility, G6PDD, sepsis, hypernatremic dehydration, hypothyroidism, cephalohematoma, subarachnoid hemorrhage, subgroup incompatibility, ABO and Rh incompatibility, and metabolic disorders. The "others" item in the study included hypothyroidism, hypernatremic dehydration, internal bleeding, metabolic disorders, and sub-blood group incompatibility.

4. Discussion

The results of the present study revealed known causes for exchange transfusion in about 50% of neonates. The most frequent known causes were ABO incompatibility, Rh incompatibility, G6PDD, sepsis, ABO and Rh incompatibility, and others (ie, hypernatremic dehydration, hypothyroidism, cephalohematoma, subarachnoid hemorrhage, subgroup incompatibility, ABO and Rh incompatibility, and metabolic disorders). Previous studies reported similar known causes, including ABO incompatibility (46%), Rh incompatibility (18%), and G6PDD (11%) (9, 11-15). Moreover, the findings of a study conducted by Bulbul et al. indicated that the most common causes of jaundice in neonates with exchange transfusion were hemolysis (56.1%) (which includes ABO blood incompatibility (23.2%), Rh incompatibility (12.3%), ABO and Rh incompatibility (5.5%), incompatibility of other blood types (2.7%), G6PDD (4.1%), sepsis (2.8%), severe dehydration (4.1%), and unknown cause (34.3%, in total 39.7%) indicated that the most common cause of jaundice in neonates with exchange transfusion was ABO incompatibility (13).

In addition, according to Bayat Mokhtari's study, the most common causes of jaundice in newborns were ABO incompatibility (43%), unknown causes (16%), Rh incompatibility (12%), G6PDD (5%), sepsis (4%), and other factors (10). Furthermore, the most common causes of jaundice in neonates reported by Behjati were ABO incompatibility (52%), Rh incompatibility (12%), and G6PDD (27%) (11). Moreover, the findings of a study carried out by Heydarian and Majdi indicated that the most common causes leading to exchange transfusion were unknown causes (25.4%), ABO incompatibility (38.1%), Rh incompatibility (16.1%), sepsis (8.5%), urinary tract infections (5.1%), G6PDD (3.4%), and other cases (3.4%), in the order of frequency (12).

Based on the results of a study performed by Badiee (14), the most common causes of jaundice requiring exchange transfusion were unknown causes (47.1%), ABO incompatibility (22.1%), G6PDD (19.1%), and Rh incompatibility (11.7%). In another study carried out by Davutoglu et al., the findings indicated that the most common causes of jaundice requiring exchange transfusions were ABO incompatibility (38%), unknown causes (13.9%), Rh incompatibility (12.6%), G6PDD (11.4%), and others (23.9%) (16). In addition, a study showed amonge neonates with a bilirubin level of > 25 mg/dL 37% had hemolytic causes versus 18% with idiopathic causes.

(2).

In the present study, blood type incompatibility was the most common cause of exchange transfusion in newborns, which is consistent with the findings of previous studies (11-14). In mothers with blood type O, anti-A, and anti-B immunoglobulin G isohemagglutinins pass the placenta and destroy A or B red blood cells. However, the existing anti-A in blood type B and the anti-B in blood type A are of immunoglobulin M type and cannot pass the placenta (16). If the mother has blood type O, the blood type of the newborn should be monitored for blood type A or B. However, since this test is usually ignored, ABO incompatibilities are not recognized, which can justify the most common cause of jaundice in neonates in this study (2).

It seems that the high incidence of jaundice requiring exchange transfusion caused by ABO incompatibility is due to the insufficient attention of gynecologists, pediatricians, and health professionals to the importance of this issue in newborns. Moreover, the provided care and preventive measures are less effective than those for patients with Rh incompatibility. In most hospitals, if the mother has blood type O, the blood type of the neonate is not checked, no precise follow-up is performed, and no serious advice is given for the follow-up of the patients. All these lead to ABO incompatibility as the most common cause of jaundice, requiring exchange transfusion in Iran.

Different countries worldwide are constantly reviewing and correcting their system of prevention, diagnosis, treatment, and follow-up regarding jaundice. Performance of the BGRh test in mothers and neonates and G6PDD in neonates and inspection of the Coombs' and Hematocrit test results of the neonates in case of incompatibility can reduce the risk of severe jaundice and its complications. Furthermore, increasing the awareness of the physicians, nurses, and families about the importance of follow-up for newborns and mothers with ABO incompatibility can lead to the decrease of jaundice and its premature treatment, which can, in turn, reduce the need for exchange transfusions.

In the present study, among the known causes, Rh incompatibility was the second frequent cause of jaundice requiring exchange transfusions. Similar results also were achieved in several other studies. If Rh-negative mothers are injected with anti-D immunoglobulin during 28 - 34

weeks of gestation or soon enough after delivery, it can significantly reduce the risk of such incompatibility. It seems that a lack of proper medical care before and after childbirth can play an important role in Rh-hemolytic disease (17).

In the present study, the third cause of jaundice requiring exchange transfusion in neonates was G6PDD. Similarly, in most previous studies, G6PDD was the third or fourth leading cause of jaundice. Based on the findings of a study performed by Yousefi et al. (18), the prevalence of G6PDD was reported to be 6.7%. In a study conducted by Abolghasemi et al. (6) on 2,000 neonates who were screened and followed up for 10 days for jaundice, the overall prevalence of G6PDD was 2.1% of the sample size. In the aforementioned study, 48.6% and 11.9% of the groups with and without G6PDD had to be hospitalized for phototherapy, respectively. Furthermore, in the aforementioned study, 11.4% and 0.9% of the groups with and without G6PDD required exchange transfusions. Based on the results of a study performed by Boskabadi et al. (19), the prevalence rate of G6PDD was reported to be 5.2%, with male predominance. However, in the aforementioned study, 29.1% and 18.7% of newborns with and without G6PDD required exchange transfusion, respectively.

Since most cases of kernicterus occur in neonates without blood incompatibility (due to proper screening for Rh and ABO blood incompatibilities), there is an increase in jaundice complications among newborns with G6PDD. The G6PDD is an X-linked recessive inheritance (20). The World Health Organization has reported the frequency of G6PDD in Iran to be within the range of 10 - 14.9%. Therefore, it is recommended to investigate the deficiency of this enzyme if the total bilirubin is above 7 mg/dL in Asian neonates and the results of their Coombs' test are negative (21). Given the higher severity of jaundice caused by Rh incompatibility, this is a reasonable procedure. However, the late diagnosis of neonatal G6PDD in Iran is probably due to the lack of routine screening of this enzyme in the first days of birth. Moreover, due to the lack of Rh or ABO incompatibility in this group, their follow-up is not taken seriously. Nevertheless, if G6PD screening becomes a routine, the patients will be diagnosed more quickly, leading to the reduction of its risks.

Although hyperbilirubinemia caused by G6PDD in neonates is well known, its physiopathology is not well understood in neonatal jaundice. Jaundice in these newborns is more likely to be due to decreased hepatic conjugation and bilirubin secretion than the increased production of indirect bilirubin caused by hemolysis (22). Moreover, in the present study, G6PDD was accompanied by genetic factors, including Gilbert's syndrome, especially in the Mediterranean race (23), which could be accountable for the lack of anemia despite the high severity of hyperbilirubinemia in the studied neonates.

In this study, sepsis caused jaundice requiring exchange transfusions in about 5% of the studied neonates. The clinical manifestations of infection in newborns can range from non-specific symptoms to severe disorders, such as fever, emesis, renal failure, and respiratory distress. However, hyperbilirubinemia can be the only manifestation of infection, especially a urinary tract infection in neonates. In addition, according to previous studies, bacterial infection was the cause of hyperlipidemia in 10% of the neonates, including urinary tract infection (8%), sepsis (1.7%), and pneumonia (0.3%), in the order of prevalence (24). Sepsis caused exchange transfusions in 4% of the newborns. In a study performed by Heydarian and Majdi (12), 8.5% of jaundice requiring exchange transfusions were caused by sepsis, out of which 5.1% were due to urinary tract infections. The possible reason for jaundice caused by sepsis in neonates could be hepatic involvement due to infection or exacerbation of hemolysis (24)

4.1. Conclusions

Based on the results, it can be concluded that the early detection and control of jaundice caused by ABO incompatibility is possible. In this regard, the education of physicians and health staff, early diagnosis of G6PDD, emphasis on the methods of prevention of Rh incompatibility and birth trauma, and early detection of detectable jaundice in midwifery can reduce the need for exchange transfusions in neonates.

Footnotes

Authors' Contribution: Study concept and design: Hassan Boskabadi and Gholamali Mamouri; Acquisition of the data: Maryam Abbasi; Analysis and interpretation of the data: Elahe Heidari; Drafting of the manuscript: Elahe Heidari; Critical revision of the manuscript for important intellectual content: Hassan Boskabadi; Statistical analysis: Maryam Abbasi; Administrative, technical, and material support: Mashhad University of Medical Sciences; Study supervision: Gholamali Mamouri.

Conflict of Interests: The authors declare that there is no conflict of interest in this study.

Ethical Approval: IR.MUMS.MEDICAL.REC.1397.466

Funding/Support: Mashhad University of Medical Sciences (approval no.: 970391)

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