Risk Factors Associated with Neonatal Jaundice: A Cross-Sectional Study from Iran

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Abstract

BACKGROUND: Neonatal jaundice is one of the main causes of the patient's admission in the neonatal period and is potentially linked to morbidity.

AIM: This study aimed to determine the possible risk factors for neonatal jaundice.

METHODS: We investigated the case of infants who were admitted to the neonatal department of Ziyaiean hospital and Imam Khomeini Hospital for jaundice. Simple random sampling was used to evaluate variables related to maternal and neonatal predisposing factors based on the medical records and clinical profiles. All variables in this study were analysed using SPSS software.

RESULTS: In this study, about 200 mothers and neonates were examined. Our findings depicted that mother's WBC, Hb, PLT, and gestational age were associated with jaundice (P < 0.05). Furthermore, there were significant relationships between different degrees of bilirubin with TSH, T4 levels and G6PD (P < 0.05). In fact, TSH, T4 levels and G6PD were found to be linked to neonatal hyperbilirubinemia. The risk factors for jaundice in our study population comprise some predisposing factors such as WBC, Hb, PLT, gestational age, TSH, and T4 levels, as well as G6PD. Neonates at risk of jaundice are linked to some maternal and neonatal factors that can provide necessary interventions to reduce the burden of the disease. Therefore, identification of associated factors can facilitate early diagnosis, and reduce subsequent complications.

CONCLUSION: Neonatal jaundice should be considered as the main policy in all health care settings of the country. Therefore, identification of factors affecting the incidence of jaundice can be effective in preventing susceptible predisposing factors in newborns and high-risk mothers.

Introduction

Neonatal jaundice is a common event that occurs especially in the first week of birth [1] [2] [3] and is one of the most common causes of hospitalisation of the term and preterm neonates in neonatal wards [1]. Based on the present evidence, 80% of premature infants have clinical symptoms, including yellowish skin and sclera, caused by serum bilirubin levels [4] [5]. Hyperbilirubinemia is a common disease that occurs especially in the first week of birth [1] [2] [3] and is one of the most common causes of hospitalisation of the term and preterm infants in neonatal hospitals [1]. It usually occurs on the second day of birth and is not usually harmful, and a self-limiting condition, where disease usually improves without treatment after reaching the normal amount of bilirubin [6] [7], but very high levels of bilirubin may lead to kernicterus as permanent brain damage. Nevertheless, diagnosis of newborn jaundice and its management will play an important role in the health of newborns [8]. If jaundice lasts more than 14 days, it is called to be prolonged neonatal jaundice [6].

An imbalance between bilirubin production and conjugation is the main mechanism of jaundice, which leads to an increase in bilirubin levels. This imbalance often occurs due to the immature liver and the rapid breakdown of red blood cells, which may be involved with several factors [9] [10] [11] [12].
The indirect bilirubin value in the physiologic jaundice of the term neonates does not exceed 12 mg/dL on the third day, and, this maximum increase reaches 15 mg/dL in preterm infants on the fifth day [13].

In physiologic jaundice, the maximum indirect bilirubin of infants who fed breast milk may be higher than those fed with skinned milk (15-17 mg/dL versus 12 mg/dL); this higher level is probably due to the lower consumption of fluid by infants who are breastfeeding [14].

Jaundice on the first day of life is always pathologic, and urgent attention is needed to find its cause. Early jaundice is often due to hemolysis and internal haemorrhage (cephalohematoma, liver or spleen hematoma) or infection. Furthermore, jaundice is considered to be pathologic after two weeks and suggests direct hyperbilirubinemia [13]. Jaundice is usually seen in newborns when the concentration of bilirubin reaches 5-10 mg/dL; however, it is seen as 2-3 mg/dL in adults. If the jaundice is observed, the total bilirubin should be measured to determine its severity. On the other hand, if the concentration in the newborn is more than 5 in the first day of life or higher than 13 mg/dL in the following days, further studies are needed to determine the direct and indirect bilirubin value, blood group, Coombs test, CBC, Peripheral blood smear and reticulocytes count [13].

Identification of predisposing factors in the management of the disease is important [15] [16]. There are a number of predisposing factors in the occurrence of this disease, including maternal diabetes, race, prematurity, height, polycythemia, male sex, cephalohematoma, medications, Trisomy 21, weight loss, breastfeeding, delayed meconium passage and family history of jaundice [17] [18] [19] [20] [21]. The most common cause of jaundice can be ABO incompatibility. Rh incompatibility and type of delivery can be among the controversial factors. Furthermore, some factors may contribute to jaundice, such as congenital infections (Syphilis, CMV, rubella, toxoplasmosis), and age more than 25 years [22]. To the best of our knowledge, there were not many studies on the epidemiology of jaundice in Iran.

On the other hand, there has also been no program for the prevention and management of jaundice. Regarding the importance of irreversible complications of hyperbilirubinemia and the prevention of these complications, the present study was aimed to investigate the predisposing factors (maternal and neonatal risk factors) in the incidence of jaundice in newborn infants admitted to Ziaeean medical centre. Identifying predisposing factors in predicting the occurrence and prevention of such risks in neonates is important to reduce the morbidity and mortality of hyperbilirubinemia.

Material and Methods

This cross-sectional study was conducted on 207 neonates (<15 days) with hyperbilirubinemia (>15 mg/dL) admitted to Ziaeean and Imam Khomeini hospitals in Tehran from April 2010 to May 2016.

All neonates were examined for neonatal jaundice risk factors. Neonates born with jaundice were selected based on the clinical outcomes of the neonates. Furthermore, data from medical records and interviews with mothers were collected by survey staff. A checklist including demographic information and other information was also provided.

Maternal variables including blood group, RH, Gestational diabetes mellitus (GDM), familial history of diabetes, history of anemia and thalassemia minor, history of thyroid disease during and before pregnancy, history of birth of a newborn with jaundice, history of smoking during pregnancy, use of herbal medicines during pregnancy, history of perinatal infections (TORCH: syphilis, rubella, toxoplasmosis), CMV, CBC were evaluated in the current study. Neonatal variables included gender, the age of birth, birth season, birth weight, blood group and Rh.

Hyperbilirubinemia was the criteria for entering this study. Also, exclusion criteria included incomplete medical records. However, 20% of the sample size was considered as additional samples in the current study.

Finally, data were collected from medical records and questionnaires. All data were then analysed by using SPSS software version 19. In this study, all principles of the Helsinki Statement were considered as a statement of ethical principles for medical studies. It is worth noting that parents were informed about the study.

20% of the extra sample size was added to prevent loss and withdrawal (N = 200). P is considered to be the first pregnancy in the formula, as reported previously (24 and 25). Thus, the sample size was calculated as 200 individuals: alpha = 0.05, Z 0.03, d = 0.03, p = 0.96, n = 165.

Data were collected by a questionnaire that was asked by the researcher from the patient. Moreover, a set of data was collected from medical records. Then, the data were analysed by SPSS software. Frequency was calculated for qualitative variables, while the mean, range and standard deviation were calculated for quantitative variables. The chi-square test was used to examine qualitative data, and t-test for non-dependent samples was used to study quantitative data. It should be noted that the P-value of < 0.05 was considered significant.
Results

The mean age of the pregnancy (weekly) based on the level of bilirubin was shown in Table 1. The result of statistical analysis indicated that the gestational age was significantly related to jaundice (P = 0.003).

Moreover, as shown in Table, the findings of the statistical analysis revealed that the birth weight of the infant was not significantly associated with the incidence of jaundice based on the bilirubin levels (P = 0.105).

Assessment of neonatal bilirubin based on the different bilirubin level revealed that total bilirubin had a significant relationship with jaundice (P = 0.000). Furthermore, there was no significant correlation between direct bilirubin with jaundice (P = 0.740).

The average reticulocyte count of the infant indicated that the reticulocyte was not significantly associated with the incidence of jaundice at the different levels of bilirubin (P = 0.079). The mean of Hb regarding bilirubin level exhibited that Hb of neonate was strongly associated with jaundice (P = 0.389). Evaluation of the mean of mcv by the level of bilirubin depicted that there was no significant difference in infant mcv in different levels of bilirubin (P = 0.107).

The mean of PLT and WBC were markedly associated with jaundice (P = 0.192; P = 0.370). The results of our study showed that the mean of Hct neonates had a significant correlation with hyperbilirubinemia (P = 0.704).

Based on the findings, it was revealed that the TSH and T4 were significantly associated with jaundice (P = 0.003; P = 0.105).

Table 2: Evaluation of Maternal Blood Groups in Different Ages of Bilirubin (bg/m)

| Total | Bilirubin | P = 0.1 |
|-------|-----------|---------|
|       | 20-24.9   | 15-19.9 | 10-14.9 |
| 99    | 54        | 19      | 26       |
|       | 27.0%     | 16.7%   | 29.0%    |
|       | 27.0%     | 13      | 10       |
| 9     | 20        | 7       | 13       |
|       | 10.0%     | 22.6%   | 8.0%     |
|       | 0.0%      | 8       | 36       |
| 44    | 45        | 1       | 8        |
|       | 22.5%     | 16.7%   | 25.8%    |
|       | 22.1%     | 11       | 31       |
| 163   | 81        | 4       | 7        |
|       | 40.5%     | 66.7%   | 22.6%    |
|       | 42.9%     | 163      | Number Total |
|       | 100.0%    | 100.0%  | 100.0%   |
|       | 100%      | 100.0%  | 100.0%   |

Based on Table 4, out of 163 patients, 41 neonates (25.2%), who their mothers suffered from GDM, exhibited a serum bilirubin level of 10-14.9, followed by a bilirubin level of 20-24.9 (16.7%) and a bilirubin level of 15-19.9 (16.1%). Neonates with different levels of bilirubin exhibited no significant difference regarding gestational diabetes mellitus (P = 0.5).

Table 5: Evaluation of Familiar Diabetes Mellitus in Different Ages of Bilirubin

| Total | Bilirubin | P = 0.2 |
|-------|-----------|---------|
|       | 20-24.9   | 15-19.9 | 10-14.9 |
| 92    | 49.5%     | 16.7%   | 54.8%    |
|       | 44.2%     | 10.0%   | 44.2%    |
|       | 56.0%     | 83.3%   | 55.8%    |
|       | 55.8%     | 31      | 163      |
|       | 100.0%    | 100.0%  | 100.0%   |

In the present study, out of 163 neonates, 72 patients (44.2%) with a history of familial diabetes revealed bilirubin levels of 10 to 14.9, following a bilirubin level of 15-19.9 (54.8%) and a bilirubin level of 20-24.9 (16.7%), (Table 5). No significant difference was found in the familiar history of diabetes among neonates with different levels of bilirubin (P = 0.2). As a matter of fact, familial history of diabetes was not found to be correlated with hyperbilirubinemia.
Bilirubin levels of 10-14.9% were seen in 9.2% of neonates with maternal thalassemia, followed by a bilirubin level of 15-19.9 (22.6%) and a bilirubin level of 20-24.9 (0%). (Table 7). The maternal thalassemia was not associated with different levels of bilirubin (P = 0.06).

We also found that the baby's blood group was not significantly related to Hyperbilirubinemia (P=0.3 Table 8), followed by a bilirubin level of 15-19.9 in 80.6% of Rh- infants and bilirubin levels of 20-24.9 in 66.7% of Rh+ infants.

Based on the data presented in Table 9, it was found that the RH blood group was not related to hyperbilirubinemia (P = 0.7).

As shown in Table 10, out of 163 patients, 50 neonates (30.7%) with asphyxia showed a bilirubin level of 10-14.9, following a bilirubin level of 15-19.9 (3.2%). There was no significant difference in asphyxia among newborns with different levels of bilirubin (P = 0.002). In other words, asphyxia was not associated with hyperbilirubinemia.

According to Table 11, 15.5% of neonates showed cephalohematoma, while 84.5% of them did not show this complication. Of the total number of 163 neonates, 13.5% of neonates with hematoma showed a bilirubin level of 10-14.9, while bilirubin levels of 15-19 and 20-24.9 were found in 25.8% and 16.7% of neonates, respectively. Findings demonstrated that there was no significant relationship between cephalohematoma and disease (P = 0.2, Table 10). In the present study, G6PD was also related to the disease (P = 0.02).

Discussion

Recent studies have demonstrated neonatal jaundice occurrence in more than 60% of term and 80% of premature neonates in the first week, where bilirubin is non-conjugate, lipid-soluble, and non-polar pigment. Bilirubin is one of the final products of haemoglobin catabolism and its clinical significance in the neonates is due to sedimentation in the skin and mucous membrane and the formation of jaundice.

This complication is also the most common cause of hospitalisation of the neonates in the first month after birth (about 19%). In most cases, jaundice can be transient, usually resolved by the end of the first week after birth, when the total serum bilirubin concentration is not considered to be a harmful condition. Severe hyperbilirubinemia has been described to develop with a potential risk for acute bilirubin encephalopathy and kernicterus [23] [24] [25] [26] [27] [28] [32] [33] [34] [35] [36] [37]. Neonatal jaundice usually starts from the face and progresses with the increase in the serum level to the abdomen and legs. Based data described before, Jaundice is one of the most common neonatal problems [23] [24]
[25] [26] [27] [28] [29].

This complication may lead to death in the first months, and infants who are still alive often suffer from mental retardation, movement and balance disorders, seizures, hearing loss at high frequencies, and speech impairment. Therefore, the timely diagnosis and treatment of neonatal jaundice are very important in preventing its complications. Identifying the predisposing factors of neonatal jaundice is still a serious discussion and can be effective in controlling jaundice and controlling the primary problem. In the natural state, since liver enzymes have not evolved enough, some icterus appears on the second to third day, reaching its maximum on the second to fourth day and decreasing on the fifth to seventh days. This type of jaundice is called physiologic jaundice. Factors such as maternal diabetes, race, premature infant, medication use of mother, male gender, cephalohaematoma, breastfeeding, weight loss, delayed stools in the baby may be correlated with physiologic jaundice [23] [24] [25] [26] [27] [28] [29] [30]. We also evaluated neonates for jaundice -specific risk association such as gestational age, birth weight gestational diabetes, familial history of diabetes, low birth weight, maternal history of anemia, maternal thalassemia, asphyxia, cephalohematoma, TSH and T4 and related blood factors including, blood count (Hb, Hct, MCV, WBC and PLT) maternal-fetal blood group and their Rh for potential risks.

The result of our study indicated that the gestational age was significantly linked to jaundice. Consist of our study; It has been described that the risk of hyperbilirubinemia significantly increases with decreasing gestational age [31] [32] [33] [34] [35]. Furthermore, weight loss in the neonatal period is considered as another risk factor for jaundice [35] [36]. Low-calorie intake has been indicated to be associated with increased hepatic circulation of bilirubin and often occurs within the first few days before milk comes in [35] [36] [37]; however, we didn’t find a significant association of birth weight with the incidence of jaundice. Based on the evidence present in literature, neonates with low gestational age (less than 37 weeks) and increased level of bilirubin in the first hours of life should be evaluated to confirm and monitor them adequately. Also, rapid diagnosis of low birth weight infants with or without visual evidence of weight loss at admission is needed to be included into clinical guideline for the control of neonatal hyperbilirubinemia [38]. Another known risk factors identified in different investigations for the development of jaundice in neonates such as Asian race, birth weight, exclusive breastfeeding, difficulty feeding, male sex, labour with oxytocin, primiparity, etc., [39] [40] [41] [42] [43] [44].

Risk factors identified in different investigations for the development of jaundice in neonates among blood count variables, the mean of Hb, Hct, PLT and WBC were found to be markedly associated with hyperbilirubinemia in the present study. However, our findings have revealed that maternal and neonatal blood group and RH were not significantly associated with hyperbilirubinemia.

A previous study indicated that blood type and Rh incompatibilities had been the important causes of kernicterus [45]. It has been depicted that ABO incompatibility, idiopathic jaundice, G6PD deficiency and Rh incompatibility be the most important predisposing factors for acute kernicterus [45].

Based on the data presented in the current study, G6PD was also related to the disease. While the exact mechanism for linking G6PD deficiency to hyperbilirubinemia is still not fully understood, early diagnosis of G6PD deficiency in infants can adequately reduce the risk of hyperbilirubinemia in affected neonates [40] [46], indicating the importance of prevention and timely treatment due to the incompatibility of ABO and Rh. According to the recommendations of the WHO Working Group, screening for all neonates should be performed in areas with a prevalence of 3-5% for G6PD deficiency [47]. It is worth noting that the incompatibility of the blood group can be managed through daily care and the diagnosis of mothers whose neonates are at risk for these disorders [40][48].

A study indicated that the main causes of the high prevalence of Jaundice complications inicteric newborns include incomplete follow-up in acrylic babies due to ABO incompatibility, physician insensitivity, lack of routine examination of neonatal babies born to mothers with type O (Rh+) and parental insensitivity [49].

Our data demonstrated that gestational diabetes mellitus was not linked to hyperbilirubinemia. Also family history of diabetes was not observed to be associated with hyperbilirubinemia.

A study has reported that gestational diabetes has various and dangerous side effects on the baby, the most common being neonatal jaundice (3.7%), [50]. It is also described that the incidence of neonatal jaundice in diabetic mothers is three times higher than that in the control group. Perhaps the reason for the difference in the prevalence of maternal diabetes associated- jaundice in different studies could be due to differences in study type and sample size [51]. In the current study, the maternal thalassemia and anaemia were not found to be associated with neonatal jaundice. However, further studies are needed to clarify the role of maternal thalassemia and anaemia in the development of hyperbilirubinemia. It is worth noting that anaemia may range from asymptomatic to life-threatening and reported to potentially be linked to severe hyperbilirubinemia [52]. Patients with haemoglobin H has been indicated to usually born with hypochromic anaemia, where may be at high risk for neonatal hyperbilirubinemia [53] [54]. Also, Based on our findings, cephalohematoma and asphyxia were not observed to be significantly linked to hyperbilirubinemia.
Neonatal asphyxia can inhibit the activity of uridine diphosphate glucuronyltransferase (UDPGT) in the liver, consequently increasing the level of unconjugated bilirubin. Cephalohematoma or ecchymosis can lead to extravascular hemolysis, consequently increasing the level of bilirubin.

A study believed that infants’ asphyxia could inhibit the activity of uridine diphosphate glucuronyltransferase (UDPGT) in the liver, leading to an increase in unconjugated bilirubin. Cephalohematoma may be associated with vascular hemolysis, resulting in elevated levels of bilirubin [55]. A study found no relationship between thyroid hormones (iodine deficiency) and jaundice [56]. However, more detailed studies are needed to evaluate the role of thyroid hormones on jaundice.

In the present study, it was revealed that the TSH and T4 were significantly correlated with the occurrence of jaundice. Our study has shown that high TSH increases the likelihood of jaundice (global statistics also indicate this); therefore, paediatricians are more interested in conducting TSH tests on the fifth day of birth and comparing with the level of bilirubin. The risk factors for jaundice in our study population comprise some predisposing Factors such as WBC, Hb, PLT, gestational age, TSH, and T4 levels, as well as G6PD. Our study may be helpful in explaining the relationship between some of the predisposing factors with newborn jaundice to provide more evidence for managing disease in hospitals. Evaluation of risk factors for neonatal hyperbilirubinemia is important because high risk factors play an important role in neonatal jaundice in a Hospital. Large-scale studies are also needed for further and also by the control group. Since the promotion of neonatal health as a vulnerable group in the health care services has a special place, so the evaluation of neonatal jaundice in all levels of health services should be considered as a fundamental policy.

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