The Frequency and Etiology of Exchange Transfusion among Hospitalized Neonates with Hyperbilirubinemia in Qom, Iran from 2001 to 2011

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Abstract: Jaundice is a common neonatal disease caused by the limited ability of a newborn to metabolize indirect bilirubin, culminating in hyperbilirubinemia. This in turn may predispose the newborn to kernicterus and other complication if not managed promptly. One of the most common management is exchange transfusion. This study aims to determine the frequency and etiology of exchange transfusion performed for neonatal hyperbilirubinemia in Qom, Iran. **Material & Methods:** In this cross sectional study, the researcher reviewed medical records of 144 newborns who underwent exchange transfusion at Children Hospital in Qom, Iran, from 2001 to 2011. Birth weight, sex, the weight before admission, serum bilirubin on admission and during exchange transfusion, gestational age, blood group and Rh of mother and newborn, complete blood count, total and direct serum bilirubin, direct Coomb's test, reticulocyte count, TSH, and G6PD activity were determined. All statistical analyses were performed using *SPSS* (Version 11.5). **Results:** Results showed exchange transfusion was performed due to ABO incompatibility (36.5%), Rh incompatibility (14.5%), G6PD deficiency (5%), G6PD deficiency and ABO incompatibility (4%), and other reasons (40%). The mean bilirubin level at admission was 27.3 mg/dl and mean bilirubin level during exchange transfusion was 26 mg/dl. The mean level of serum bilirubin was 27.3 mg/dl on admission and 26 mg/dl during exchange transfusion. Symptoms of kernicterus appeared in 10 newborns, out of whom 5 (50%) were due to ABO incompatibility, 1 due to Rh incompatibility (10%), 1 due to Rh incompatibility (10%), and 3 (30%) for other reasons. **Conclusion:** Early detection of ABO and Rh incompatibility and G6PD deficiency in the affected newborns may be important for reducing the risk of severe hyperbilirubinemia, kernicterus, and the need for exchange transfusion.

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Introduction

Neonatal jaundice is a common but benign problem which affects more than 60% of term newborn and 80% of pre-term newborns in the first week of life. Without treatment, the disease can be extremely toxic for brain cells (1, 2). Several factors should be considered in neonatal jaundice such as first-day jaundice, family history of jaundice, blood incompatibility, Rh, ABO, G6PD deficiency, history of diabetic mellitus in mother, prematurity, cephalhematoma, polycythemia, and history of breastfeeding. Abnormal jaundice occurs during the first 24 hours or persists after 14 days. Bilirubin level higher than 12 mg/dl and above 10 – 14 mg/dl is abnormal in term and preterm neonates respectively. The rising serum bilirubin rate faster than 5 mg/dl during 24 hours, or the direct bilirubin above 2 mg/dl are signs of abnormal jaundice as well. Some causes of abnormal jaundice include Rh and ABO incompatibility, and also G6PD deficiency. ABO incompatibility is one of the most common causes of neonatal hyperbilirubinemia (1, 3, 4, 5, 6) and affects newborns with A or B, and mothers with O blood groups (1, 6). Rh incompatibility happens in newborns with positive Rh whose mother's have a negative Rh (1). Another causing factor is G6PD deficiency, which is a genetic enzyme deficiency and most common in male. The male to female ratio in Iran is 3/1 (7) and prevalence of this disease, reported by WHO is 10 to 14% (7). Jaundice is the hallmark of indirect hyperbilirubinemia, which first appears in the face and then gradually progresses to the abdomen and feet. By observing the affected zone, the bilirubin level can be roughly estimated. However, this is not reliable and a serum bilirubin test is necessary. Bilirubin concentration is approximately 5, 15, and 20 mg/dl in the face, abdomen, and sole, respectively. One of the critical complications of hyperbilirubinemia which is caused by the precipitation of bilirubin in the brain is kernicterus. When indirect bilirubin is higher than 21 to 50 (average 30) mg/dl, it may precipitate in the brain especially in basal ganglia and cause kernicterus. In premature newborns, this disorder may occur even at lower bilirubin concentrations of 8 to 12 mg/dl (1). Kernicterus signs include lethargy,

poor feeding, respiratory distress, high-pitched cry, bulge fontanel, and hypotonia (1, 8).

Not measuring bilirubin after the first 24 hours of birth, early discharging of newborns from the hospital (sooner than 48 hours), ignoring parents' complaints about jaundice, not identifying important risk factors of jaundice, and delayed treatment contribute in developing these complications (1).

The goal of therapy is prevention of rising bilirubin up to dangerous level. Methods of treatments include phototherapy, exchange transfusion, administration of IVIG and Sn - protoporphyrin.

Treatment initiates by phototherapy, and if it fails to reduce bilirubin or symptoms of kernicterus arise, the last step will be exchange transfusion (1). This is the standard treatment for curing hyperbilirubinemia and preventing kernicterus (9, 10). Regarding the high prevalence of hyperbilirubinemia in newborns and its hazardous complications such as the RBC destruction in ABO and Rh incompatibility, G6PD deficiency, anemia, precipitation of bilirubin in the brain and kernicterus, and other reasons such as blood and urinary tract infections put the newborn's life at risk. One of the most effective treatments is exchange transfusion. The purpose of this research is to determine the frequency of exchange transfusion reasons and kernicterus in newborns with hyperbilirubinemia admitted to Oom[.s] children medical center during 2001 to 2011. Afterwards, appropriate measures and recommendations to prevent jaundice and treat newborns are proposed.

Methods

This study reviewed 144 newborns' record files with hyperbilirubinemia who were treated by exchange transfusion with hyperbilirubinemia in Children Hospital, Qom, Iran, between 2001 to 2011. The data comprised 15 factors, all recorded on a checklist, and included birth weight, admission weight, sex, bilirubin level on admission and during exchange transfusion, pregnancy age, cephalohematoma, blood group and RH of the mother and the newborn, total blood cells count, total and direct serum bilirubin levels, direct Coomb's test, reticulocyte level, serum TSH and G6PD activity. ABO incompatibility was taken into account solely for those newborns with A or B blood group whose mother's had group O. Rh incompatibility was recorded only for newborns with positive Rh whose mother's was negative. The diagnosis of kernicterus made in the base of clinical manifestation such as hyporeflexia, lethargy, poor feeding, respiratory distress, high-pitched cry, bulge fontanel, and hypotonia in the absence of other reasons. All statistical analyses were conducted using *SPSS* (Version 11.5). After calculating the frequency of each variable, a bivariate analysis was carried out through a *t*-test and a Pearson correlation test. The *p* was considered significant at <.0.5.

Results

In this study, out of a total 144 newborns, 63 (44%) were girls while 81 (56%) were boys. 36.5% of newborns studied (52 cases) have treated by exchange transfusion due to ABO incompatibility, 14.5% (21 cases) due to Rh incompatibility, 5% due to G6PD deficiency, 4% due to ABO incompatibility and G6PD, and 40% (57 cases) due to other reasons (Table 1). As for the blood groups of the newborns, 51 cases (35.5%) had group O, and nine cases (6.5%) had AB. Blood group A comprised 39 cases (27%) and blood group B 44 cases (31%) which play a key role in ABO incompatibility. 8% of patient were RH negative while 92% were positive. The birth weight of newborns was at least 900 g and at most 4,500 g, with a mean of 2,685 g and an *SD* of 765. 672. Their admission weight was least 900 g and at most 4,300 g, with a mean and *SD* of 2,604.5 g and 768. 682, respectively. The serum bilirubin level of newborns during hospitalization was 12 mg/dl minimum and 50 mg/dl maximum, with a mean of 27.3 mg/dl and a *SD* of 5.85153. Serum bilirubin level during exchange transfusion was 13.2 mg/dl minimum and 42 mg/dl maximum with a mean of 26 mg/dl and *SD* of 5.85153. G6PD deficiency was detected in 13 cases (9%) (Table 2) according to low G6PD activity. One of them was female. Using *t*-test, the mean serum bilirubin level of newborns with normal G6PD activity and G6PD deficiency was 27 and 31 mg/dl, respectively. The difference was statistically significant (p =.03). Conducting *t*-test again, the mean of serum bilirubin level and the *SD* of newborns with normal G6PD and G6PD deficiency at exchange transfusion were calculated. The results were 25.5 mg/dl and 5.40499 for the first group and 32 mg/dl and 6.64724 and for the second group. This was statistically significant at p =.004. The gestational age was at least 26 and at most 40 weeks, with an average of 36 weeks and three days and an *SD* of 3.838. 15(10.4%) of patients were coomb's positive. All of them had RH incompatibility. Using *t*-test, the mean hemoglobin of newborns with positive Coomb's test and negative Coomb's test were 10.5 and 15.2 g/dl, respectively, with corresponding *SDs* of 1.29499 and 2.78958 (p =.001). The hemoglobin level in group with ABO incompatibility was at least 9.7 g/dl and at most 23 g/dl, with the mean of 15.3 g/dl and the *SD* of 2.88645. The reticulocyte count of newborns with ABO incompatibility was at least 0.2% and at most

24% with, with the mean of 3.5% and the *SD* of 3.66158. In addition, minimum level of hemoglobin in newborns with Rh incompatibility was at least 8.8 g/dl and maximum level was 18 g/dl, with the mean of 13.6 g/dl and the *SD* of 2.88645. The reticulocyte level of the same newborns was 0.5% minimum and 5.5% maximum, with the mean of 2.5% and the *SD* of 3.66158. None of the infants had cephalhematoma and the history of jaundice in their families was about 3%. On hospitalization day, minimal age of newborns was one day and maximal age was 16 days, with the average of five days and 12 hours and the *SD* of 2.723. Kernicterus was detected in 10 cases, five cases had ABO incompatibility, one case had G6PD deficiency, one case had Rh incompatibility, and three cases had other reasons.

Discussion

Indirect hyperbilirubinemia is a common condition in neonatal period. It may be occur in the majority of term and pre-term newborns and may be caused by Rh or ABO incompatibility and G6PD deficiency and some other reasons. In severe cases, it may cause severe and acute hemolysis and develop severe anemia and kernicterus. Therefore, by performing treatments such as phototherapy and exchange transfusion such risks can be eliminated. In this study we investigated the frequency of exchange transfusion reasons in newborns with hyperbilirubinemia who were admitted to children Hospital, Qom, Iran, from 2001 to 2011. In this study, the most common cause of exchange transfusion was ABO incompatibility. The data came from the records of those newborns with A or B blood group whose mothers' was O. This was taken into consideration in other studies (2, 8, 11, 12), too. The second cause of exchange transfusion was RH incompatibility with 61(40.5%) of patients and the third reason was G6PD deficiency with 13(9%) cases. One of 13 cases with G6PD deficiency, was female. This findings are consistent with other studies (13, 14, 15, and 16) in which boys were found to be predominant. In other hand, G6PD deficiency is sex-related, and the proportion of boys to girls is three to one in our country. In girls, G6PD can be due to the Lion phenomenon and inactivation of an X chromosome. Maximal serum bilirubin of newborns with G6PD deficiency was 31 mg/dl, which was higher than the normal group (27mg/dl), which was significant statistically (p =.03). These conditions indicate an acute and severe hemolysis, which is caused by the destruction of RBC in the reticuloendothelial system, because of G6PD enzyme deficiency and is consistent with other studies. 10 cases of kernicterus were reported, 50% of them were due to ABO incompatibility, 10% due to G6PD incompatibility, 10% due to Rh incompatibility, and 30% for other causes. The most common reason of kernicterus was ignoring neonatal jaundice, and early discharge from the hospital. In another study, 5 cases (7.3%) of 68 newborns under exchange transfusion were diagnosed with kernicterus. Kernicterus was seen bilirubin level of higher than 30 mg/dl. The mean of hemoglobin in the cases with positive Coomb's tests was 10.5 g/dl and in negative Coomb's tests was 15.2 g/dl, which is indicative of anemia. In Ozolek study the same result was reported (17).

Conclusion

It was found that the most common reason of exchange transfusion in newborns with hyperbilirubinemia were ABO incompatibility. Rh incompatibility and G6PD deficiency ranked second and third. Further, what most predisposed newborns to kernicterus was parents' negligence or unconcern about their infant's jaundice. Therefore, by promptly identifying the mother's and the newborn's blood group and Rh, measuring G6PD activity, raising parents' knowledge about jaundice, preventing early discharge, and observing the newborn up to 48 hours after discharge, the need for exchange transfusion and the occurrence of kernicterus can be eliminated.

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