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Risk Factors of Severe Hyperbilirubinemia in Neonates Undergoing Exchange Transfusion in Imam Reza Hospital Kermanshah- Iran, during 2012 to 2016

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Abstract

Background
Jaundice is one of the most common problems in neonatal period. Although the efficacy of exchange transfusion in the treatment of neonatal jaundice is known and quickly reduces blood bilirubin levels, but severe neonatal hyperbilirubinemia is associated with significant morbidity and mortality. We conducted this study to investigate the risk factors of severe hyperbilirubinemia in neonates undergoing exchange transfusion in Imam Reza Hospital Kermanshah, Iran.

Materials and Methods
In this retrospective study, records of newborns with hyperbilirubinemia who were undergoing exchange transfusion to Imam Reza hospital in Kermanshah from of 2012 to 2016 were studied. Information were extracted from the patient case and recorded in the data collection form. Data analyzed using SPSS software (version 24.0).

Results
Birth weight of 42.1% of neonates was less than 2,500 gr and 43.1% were preterm. The most common causes of severe hyperbilirubinemia including: unknown causes (42.2%, n=38), ABO incompatibility (27.8%, n=25), and sepsis (12.2%, n=11). The most common complications of exchange transfusion in this study were thrombocytopenia (33.4%), hypocalcaemia (18.7%), hyperglycemia (12.3%), and hypoglycemia (12.3%).

Conclusion
According to the results, major risk factors for the occurrence of severe hyperbilirubinemia in neonates were birth weight less than 2,500 gram, gestational age below 37 weeks, age less than 5 days, and weight loss more than 10% of birth weight at the time of admission.

Key Words: Exchange transfusion, Hyperbilirubinemia, Neonate, Risk factor.

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1- INTRODUCTION

Neonatal hyperbilirubinemia is the most common morbidity in neonatal period. Visible jaundice is seen in approximately 60% of term infants and 80% of preterm infants during the first week of life. Neonatal jaundice is the most common reason for hospitalization of infants in the first month of birth (1, 2). In Iran, hyperbilirubinemia is the cause of hospitalization in 32% of admitted neonates annually (3). Severe jaundice was diagnosed when a newborn infant had a peak bilirubin level ≥ 342 μm (20.0 mg/dL) in serum within 10 days of birth; severe jaundice is a serious potential cause of permanent brain damage, kernicterus, which is characterized by cerebral palsy, impaired mental development, and neurological deafness (4).

Increased bilirubin over 25 mg/dl affects the Intelligence Quotient (IQs) of term and healthy infants. Also, neonatal jaundice is one of the common causes of preterm neonatal auditory disturbance and an important cause of hearing loss in children, especially in developing countries (5). For preventing kernicterus and other complications of hyperbilirubinemia, jaundice should be managed by phototherapy or exchange transfusion or the use of phototherapy together with some herbal medicines such as Chicory extract bath (6, 7). Also, in recent years, the tendency to use drugs has been increasing in the treatment of neonatal jaundice, for example Zinc Sulfate (8, 9).

Exchange transfusion (ET) is required in approximately 10% of hyperbilirubinemic hospitalized neonates (10). The importance of this disease is not only due to the economic, social and psychological consequences of the hospitalization of the newborn, but also because of the chronic complications of the disease on the nervous system and its high morbidity (1).
The most common cause of jaundice in the neonatal period is usually due to hemolysis from genotypes AO, BO, OO of blood group (ABO) incompatibility. Rhesus (Rh) incompatibility, glucose-6 phosphate dehydrogenase (G6PD) deficiency, polycythemia, cephalhematoma, sepsis, hypothyroidism, infections, metabolic disorders, congenital malformations, prematurity and breast-feeding jaundice are the other causes (11, 12). ET has an important role in preventing kernicterus in the treatment of indirect hyperbilirubinemia of the newborn (4, 13, 14). Usually, treatment of indirect hyperbilirubinemia begins with phototherapy and if, despite treatment with phototherapy, the level of bilirubin increased (failure of treatment with phototherapy), or, initially, the serum bilirubin level is greater than the acceptable level for the age and weight of the newborn according to the American Academy of Pediatrics protocol (2004), exchange transfusion is done (15, 16).

Severe hyperbilirubinemia is mainly treated by Exchange Transfusion. According to American Academy of Pediatrics (AAP), in healthy term neonates with birth weight ≥ 2500 grams, ET is indicated when indirect bilirubin level reaches≥ 25 mg/dl and in cases with risk factors or gestational age of 35-37 week and well ET is indicated when indirect bilirubin level reaches ≥ 20 mg/dl despite 6 hours of intensive phototherapy. In newborns of 35-37 week and with risk factors, ET is indicated when the indirect bilirubin level reaches ≥ 18 mg/dl despite 6 hours of intensive phototherapy (17).

Exchange transfusion is a standard treatment for immediate reduction of serum bilirubin levels and prevention of kernicterus, and includes replacing more than 90% of the infant's blood volume with one or two donor blood (18, 19). Although the value of ET in the treatment of neonatal hyperbilirubinemia is recognized, the procedure is associated with serious adverse events that carry a risk of both

mortality (0.1-0.5%), and morbidity (2.8 to 5.2%) in term neonates (20-22). ET is associated with many complications such as hypersensitivity reactions, sepsis, catheter-induced vascular damage, hypotension, necrotizing enterocolitis, etc. (23). The potential complications of exchange transfusion are important and are divided into three groups: 1- Complications associated with blood components such as: excessive heparinization (High Heparin Usage), Graft Versus Host Disease (GVHD), hemolysis due to incompatible red blood cells, hyperkalemia, hypocalcemia, hypoglycemia, tetany, thrombocytopenia and infections. 2- Complications associated with catheter include: Cardiac arrhythmias, embolism, infection, Necrotizing Enterocolitis and Thrombosis. 3- Complications associated with operation of exchange transfusion such as: sudden bleeding, air embolism, hemolysis due to mechanical damage, hypothermia, intracerebral hemorrhage, intracranial pressure instability, and systemic blood pressure instability due to hypovolemia or hypervolemia (24).

Even in developed countries, there were still several reports of newborn deaths from severe hyperbilirubinemia or complications of ET. In study by Yu Canfeng et al. identified adverse events secondary to ET included thrombocytopenia (54.6%), hyperglycemia (42.8%), apnea (3.3%), and necrotizing enterocolitis (NEC) (1.3%) (5). Also, result study of Ballot and Rugamba showed six of these babies (6/26; 23.0%) had signs of kernicterus. The most significant complication of exchange transfusion was apnoea requiring mechanical ventilation in three patients (3/64; 4.6%) (25). In Iran, in a study conducted by Boskabadi et al. (2015) in Mashhad, the risk factors of jaundice in newborns including unknown causes, ABO, RH, G6PD and sepsis have been reported (26). In another study by Alizadeh Taheri and his colleagues (2014) on 94 neonates with hyperbilirubinemia lead to exchange transfusion, the results showed that the most important risk factors included premature labor, breastfeeding jaundice, ABO incompatibility and G6PD (27). Eghbalian (2007) showed that the most complications of exchange transfusion in neonates were thrombocytopenia (51.7%), and hypocalcaemia (30.8%), and the frequency of death due to exchange transfusion was reported as 5% (28). However, exchange transfusion is an invasive therapeutic procedure and has many risks and complications. But on the other hand, sever hyperbilirubinemia also has its own complications. Therefore, it is possible to identify the causes of hyperbilirubinemia and the complications of exchange transfusion by preventing these complications. By preventing these factors, contributes to the health of the newborns and future generations of the community. We conducted this study to investigate the risk factors of severe hyperbilirubinemia in neonates undergoing exchange transfusion in Imam Reza Hospital Kermanshah (Iran), from 2012 to 2016.

2- MATERIALS AND METHODS

2-1. Study design and population

In this retrospective study, the medical records of hyperbilirubinemic infants who were admitted to Imam Reza hospital in Kermanshah (Iran) from 1st of January 2012 to 31st of December 2016 and undergoing exchange transfusion were evaluated. In this study, 90 neonates with severe hyperbilirubinemia undergoing exchange transfusion were evaluated.

2-2. Methods

In this study, evaluated of newborns with severe hyperbilirubinemia and undergoing exchange transfusion. The mean of severe hyperbilirubinemia is bilirubin more than

95 percentile on the hour-specific Bhutani nomogram, in accordance with the American Academy of Pediatrics protocol (2004) (13). All the neonates studied received phototherapy immediately after admission, and total serum bilirubin was measured 6 hours after initiation of phototherapy.

2-3. Measuring tools

Demographic data (gender, age, birth weight, gestational age, etc.), cause of hyperbilirubinemia and complications of exchange transfusion were collected from hospital records of neonatal care unit. To ensure the accuracy of the information and in cases where their information was incomplete was contacted with the families of infants and their physician. Then data was recorded in the data collection form. Then data was gathered and recorded by the trained researcher in the data collection form and data analyzed by statistics consultant and using SPSS software version 24.0. Multiple linear regression analysis was used to express related factors.

2-4. Intervention

In the neonatal intensive care unit, phototherapy is used to treat hyperbilirubinemia **Figure.1**, and in severe hyperbilirubinemia, exchange transfusion is used **Figure.2**. Collected information includes the risk factors for jaundice, such as: neonatal weight, gestational age, blood incompatibility, infection, etc., and complications of exchange transfusion including: mortality, arrhythmia, hypocalcemia, thrombocytopenia, infection, etc.

Complications related to exchange transfusion included: hypocalcemia (serum calcium concentration less than 8 mg/dl in term infants and less than 7 mg /dl in preterm infants), hyperkalemia (serum potassium concentration greater than 5.5 mmol/L), hypoglycemia (plasma glucose concentration less than 40 mg/dl), thrombocytopenia (less than 150,000 platelet counts), sepsis (clinical signs of infection + positive blood culture), necrotizing enterocolitis (including abdominal distention and radiographic symptoms), cardiac arrhythmias and eventually death.

Fig1: Phototherapy in neonates.

Fig.2: Exchange transfusion in neonates.

2-5. Ethical consideration

Initially, the researcher obtained the necessary license from the deputy of the Kermanshah University of Medical Sciences. Then, the purpose of the research was explained to the parents and they were assured that their information would remain confidential. Also, all ethical principles in the use of resources for study were observed.

2-6. Inclusion and exclusion criteria

The inclusion criteria included all infants requiring exchange transfusion due to severe hyperbilirubinemia more than 95 percentile on the hour-specific Bhutani nomogram, in accordance with the American Academy of Pediatrics protocol (2004) (13). Exclusion criteria included the discharge of infants with parental consent.

2-7. Data Analyses

Then, data were analyzed by SPSS software version 24.0 using statistical tests. The mean and standard deviation and frequency (percent) were used to analyze the descriptive statistics. Regression analysis was used to investigate the factors associated with severe hyperbilirubinemia.

2-3. Laboratory measurements

Laboratory measurements include the risk factors for jaundice, such as: neonatal weight, gestational age, blood incompatibility, infection, etc., and complications of exchange transfusion including: mortality, arrhythmia, hypocalcemia, thrombocytopenia, infection, and etc. Complications related to exchange transfusion included: hypocalcemia, hyperkalemia, hypoglycemia, thrombocytopenia, sepsis (clinical signs of infection + positive blood culture), necrotizing enterocolitis, cardiac arrhythmias and eventually death.

3- RESULTS

The purpose of this study was to investigate the risk factors of severe hyperbilirubinemia in neonates undergoing exchange transfusion in Imam Reza Hospital Kermanshah (Iran), from 2012-2016. Of the 90 infants admitted with severe hyperbilirubinemia and undergoing exchange transfusion in this 5 year period, 51.1% were boys and 48/9% were girls. Also, 64.4% of the infants were less than 5 days old. The weight of 42.1% of them was less than 2,500 grams; 39 infants

(43.3%) were the first child and 38 infants (43.1%) were preterm (gestational age was less than 37 weeks). In this study, 47.8% of neonates were born by Normal Vaginal Delivery (NVD), and 100% of infants had exclusive breast feeding. At the time of admission 72.2% of the newborns had a weight loss of more than 10% of birth weight **Table.1**. Chi-square test did not show significant differences between gender in the ratio of male and female neonates (P = 0.833). Also, the results of Chi-square test showed no significant difference in the age of infant on admission and the exchange transfusion (P=0.107), and more than 64% of the newborns had an exchange transfusion at the time of hospitalization less than 5 days.

The binomial test result showed that there was a significant difference between weight losses in newborns and need to exchange transfusion. Weight loss of more than 10% of the birth weight was determined in 50% of neonates underwent exchange transfusion (P= 0.001). In the present study more common causes of severe hyperbilirubinemia were, 38(42.2%) unknown causes, 25(27.8%) ABO incompatibility, 5(5.6%) Rh incompatibility, 8(8.9%) G6PD deficiency, 11(12.2%) sepsis, 3(3. 3%) Urinary Tract Infection, respectively **Figure.3**. The results of multiple linear regression analysis showed that, in the presence of other variables, the bilirubin level in newborns with G6PD deficiency was 7.35 more than those without deficiency. The relationship of other risk factors is reported in **Table.2**. The results of this study showed that thrombocytopenia (33.4%), hypocalcaemia (18.7%), hyperglycemia (12.3%), and hypoglycemia (12.3%) were the most frequent complications in the neonates undergoing exchange transfusion. No cases of apnea, Necrotizing Enterocolitis (NEC), and mortality have been observed **Figure.4**.

The complications of exchange transfusion in boy neonates were more than in girls neonates (P<0.05). The results of the study, using chi-square test, showed that the complications of exchange transfusion were statistically significantly lower in normal birth weight (2,500-4,000 gr) than in neonates with low birth weight (< 2,500 gr) (P<0.05) **Table.3**.

Table-1: Baseline Demographic Characteristics of newborns has undergoing exchange transfusion

Demographic Characteristics	Frequency	Percent
Gender:		
1. Boy	46	51.1
2. Girl	44	48.9
Gestational age(preterm, under 37 weeks)	38	43.1
1. Boy	20	52.6
2. Girl	18	47.3
Age of infant on admission (under 5 days)	58	64.4
Birth weight (less than 2,500 grams)	38	42.1
First child	42	43.3
Type of feeding (breast milk)	90	100
Maternal delivery mode (NVD)	53	58.8
Weight loss (more than 10% of birth weight at the time of admission).	65	72.2

NVD = Normal Vaginal Delivery.

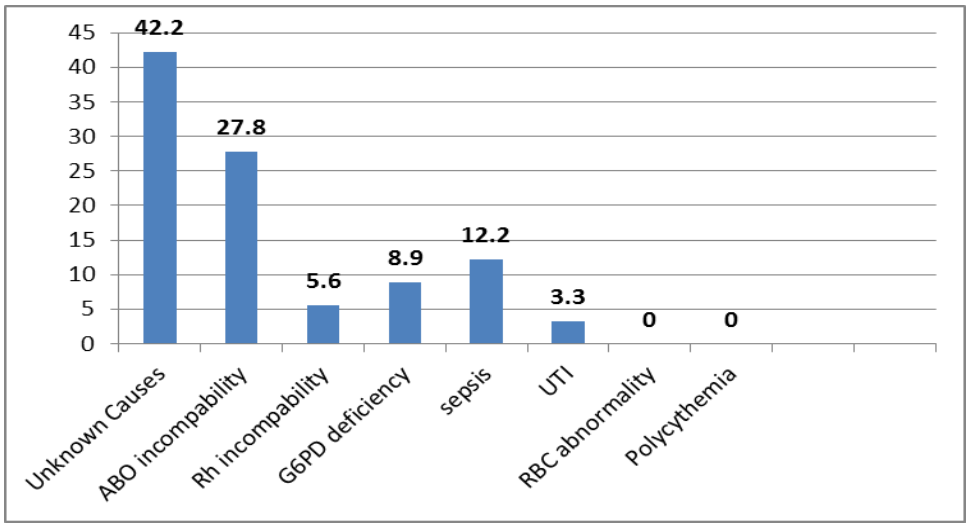

Fig.3: Frequency of causes of hyperbilirubinemia in neonates undergoing exchange transfusion in Imam Reza Hospital Kermanshah-Iran, from 2012 to 2016 (in term of percentage). UTI**:** Urinary Tract Infection.

Table-2: Bilirubin Predictive Factors by Multiple Linear Regression Model.

Variables	Beta coefficient	S.E	P-value	95%CI
ABO	1.76	1.86	0.349	-1.95 - 5.47
G6PD	7.35	3.02	0.017	1.33 - 13.37
RH	3.93	3.77	0.301	-3.58 - 11.44
Weight Loss	-1.59	1.94	0.416	-5.47 - 2.28
UTI	0.86	4.86	0.859	-8.81 - 10.55
Sepsis	3.40	2.55	0.186	-1.67 - 8.48
Unknown Causes	26.49	3.59	<0.001	19.33 - 33.65
S.E: Standard Error; CI: Confidence Interval.				

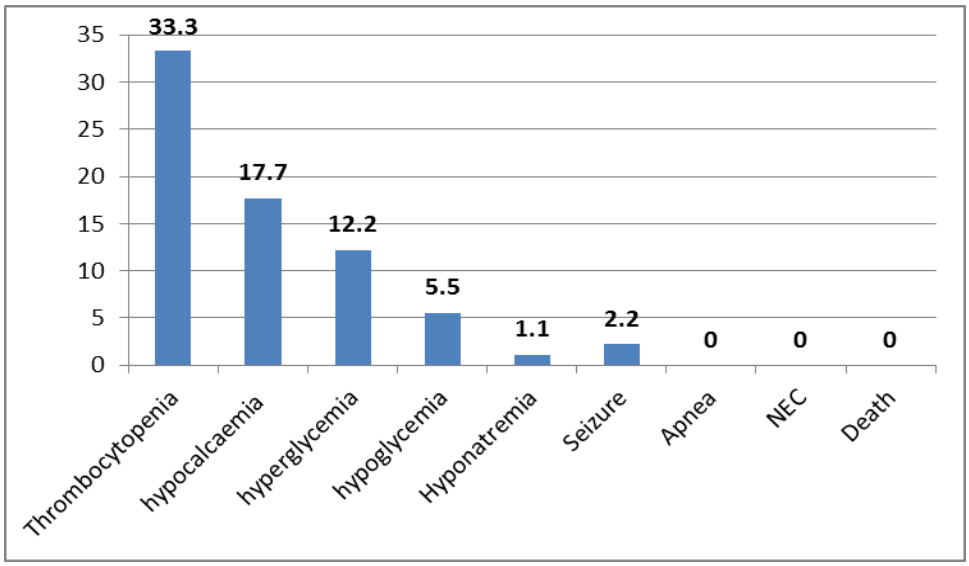

Fig.4: Frequency of exchange transfusion complications in neonates undergoing exchange transfusion in Imam Reza Hospital Kermanshah-Iran from 2012 to 2016 (in term of percentage). NEC: Necrotizing Enterocolitis.

Table-3: The frequency of complications of exchange transfusion according to birth weight

Birth weight (gr)				
Complicated/ Uncomplicated	Less than 2,500 Number (percent)	2,500 to 4,000 Number (percent)	Total Number (percent)	P-value
Complicated	29 (76.3%)	24 (46.1%)	54 (58.8%)	0.001
Uncomplicated	9 (23.7%)	28 (53.8%)	37 (41.1%)	
Total	38 (100%)	52 (100%)	90 (100%)	

4- DISCUSSION

In this five years study, 90 newborns have undergoing exchange transfusion due to severe hyperbilirubinemia. Major risk factors for the occurrence or exacerbation of hyperbilirubinemia in this study were birth weight less than 2,500 gr, gestational age below 37 weeks, first born, infant's age less than 5 days at admission, breastfeeding, NVD (it may be due to early discharging of neonates with NVD than cesarean section), and the presence of hematomas such as cephalohematoma in NVD and weight loss more than 10% of birth weight at the time of admission.

Kalkan et al., in evaluating 185 neonates admitted with hyperbilirubinemia, showed that the factors effecting to jaundice including Male sex, preterm births, breastfeeding, and weight loss were significant (29). In study of Najib et al., factors such as male sex, NVD, and breastfeeding have been reported as a risk factor for hyperbilirubinemia (30). However, in the study of Jalali et al. regarding the effective factors in neonatal hyperbilirubinemia in university hospitals in Northern Iran, there was a significant difference in neonates in terms of sex, type of delivery, breastfeeding and weight loss more than 10% in newborns (31); however, the cause of this difference is unknown and needs further investigation.
This study did not show a significant difference in the ratio of boys and girls undergoing exchange transfusion, which is consistent with the results of the study by Boskabadi et al. (26), and the study of Eghbalian et al. (28), and Nabavi et al. (32); but, Kalkan et al. (29), and Najib et al. (30) showed that there is a significant relationship between the factors contributing to jaundice and the gender of the boy, and the results of the present study contradict these studies. The results of the present study showed that more than 64% of neonates undergoing exchange transfusion were less than 5 days of age. In the study of Mahmud Hossain et al. (2015), similar results were achieved and the mean age of infants admitted to Hyperbilirubinemia was 5 days (33).

In our study, it was found that more than 57% of neonates undergoing exchange transfusion were over 37 weeks old. Although age below 37 weeks or prematurity is a risk factor for hyperbilirubinemia, but the reason is the result of our study most infants below 37 weeks were admitted to the Neonatal Intensive Care Unit (NICU), and hyperbilirubinemia is rapidly diagnosed and they were treated and they did not need to exchange transfusion. In the study of Jalali et al. (31), Nabavi et al. (32), and Shayan et al. (34), also obtained similar results; but the results of some studies, such as the study by Boskabadi et al. (26), and Alizadeh Taheri et al. (27) contradicted this study and the mean gestational age of infants in these studies was below 37 weeks. Results of our study showed that over 60% of neonates undergoing exchange transfusion weighed

more than 2,500 grams which is consistent with the study by Esfandiarpour et al. (35), Canfeng Yu et al. (5), and Ballot et al. (26); but it contradicts the study of Alizadeh Taheri et al. (27). This difference may be due to the fact that in our study, most infants with birth weight less than 2,500 grams were admitted to the NICU and hyperbilirubinemia was rapidly diagnosed and with the onset of phototherapy, exchange transfusion were prevented. The results of this study showed that a significant difference in weight loss in the studied neonates; weight loss of more than 10% of the birth weight was determined in 50% of neonates underwent exchange transfusion which is consistent with the study by Esfandiarpour et al. (35), and the study of Boskabadi et al. (36). The results of the study by Beskabadi et al. (2014) showed that about one thirds of neonates presenting with idiopathic hyperbilirubinemia had severe weight loss and hyperbilirubinemia was also more severe in this group. The average weight loss in the neonates with severe hyperbilirubinemia (> 20 mg/dl) was three times that of moderate hyperbilirubinemia (< 20 mg/dl) (37).

In the present study, the factors affecting the incidence of hyperbilirubinemia were respectively: an unknown causes, ABO incompatibility, Rh incompatibility, G6PD deficiency, sepsis, and urinary tract infection. The results of our study are consistent with the study of Beskabadi et al. (26), Alizadeh Taheri et al. (27), and Najib et al. (30). In a study by Ballot et al., the prevalence of causes of severe hyperbilirubinemia, Isoimmune haemolysis, ABO incompatibility, Rh incompatibility, cephalhaematoma, red cell membranopathy, severe intraventricular haemorrhage, was reported (24). In the study of Jalali et al., Rh incompatibility, ABO incompatibility, G6PD deficiency and History of phototherapy in siblings were the most common causes of severe hyperbilirubinemia (31). For unknown cases, Breast milk Jaundice is thought (because 2% of mature neonates with feeding breast milk after the first 7 days of birth) (17). From other unknown causes, the incompatibility of blood subgroups may be one of the most important ones. In the present study, the most complication in the neonates was thrombocytopenia, hypocalcaemia and hyperglycemia, respectively. No cases of apnea, NEC, and mortality have been observed, which is consistent with the study by Canfeng Yu et al. (5), and the study of Eghbalian (28). In the study of Esfandiarpour et al., the most common complication of exchange transfusion, sepsis, seizure, hypoglycemia and apnea were reported (35).

In a study by Ballot and Rugamba, apnea requiring mechanical ventilation and glucose instability has been reported as complications of exchange transfusion (25). The most common complications of exchange transfusion, metabolic acidosis and thrombocytopenia were reported in the study of Shayan et al. (34). Also, the results of this study showed that the complications of exchange transfusion in neonates with low birth weight (less than 2,500 grams) were higher than those with normal birthweight (2,500-4,000 grams); which was consistent with Shayan et al. (34). The most important complication in our study was thrombocytopenia, which is probably due to the fact that the replacement of blood in the exchange transfusion neonates in this center does not use whole blood and Packed Red Blood Cell and Fresh and Frozen Plasma (FFP) are used simultaneously.

4-1. Limitations of the study

One of the limitations of this study was the lack of control group to evaluate jaundice risk factors. On the other hand, in our study, the most common cause of neonatal hyperbilirubinemia was unknown causes, which could not be verified due to the retrospective of this study. Also, being a

retrospective study and the small number of data in the study may limit the results for generalization. Therefore, wider studies with comparative or prospective methods and with more complete variables will help to better understand the major and minor risk factors and prevent its consequences.

4-2. Recommendations

Given the significant difference in the weight loss of newborns, it is recommended that mothers breastfeed the infant every 2 or 3 hours in the first few days of the birth of the newborns (8 to 12 times in 24 hours), and teaching how to breastfeed to infants before giving birth. Avoid wearing too much clothing to the newborns. Also, the environment temperature is not too high for the infant because of the high insensible water loss and weight loss of the infant. Avoid giving supplements like sugar juice because it reduces breast milk volume.

5- CONCLUSION

The results of this study showed that major risk factors for the occurrence of severe hyperbilirubinemia were: birth weight less than 2,500 gram, gestational age below 37 weeks, first born, infant's age less than 5 days at admission, NVD and weight loss more than 10% of birth weight at the time of admission. Also, the most common complications of exchange transfusion in this study were thrombocytopenia, hypocalcaemia, hyperglycemia and hypoglycemia.

By educating the newborns families about early diagnosis of jaundice and identifying some factors requiring pre-discharge follow-up, such as hemolytic agents, especially those with risk factors for hyperbilirubinemia, can greatly help to reduce the rate of exchange transfusion and its complications. No discharge high-risk infants until their jaundice situation is cleared and the codification of proper infant's follow-up system is also likely to be effective. On the other hand, according to the results of this study, and considering that the common causes of hyperbilirubinemia, ABO incompatibility is suggested that mothers with a special blood type O positive (because they have Rh incompatibility) should be trained in the first few days after the birth of the infant, as soon as the infant is icteric, and before the jaundice increases, visit the doctor to preventing neonates exchange transfusion by controlling the level of bilirubin.

6- CONFLICT OF INTEREST: None.

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8- REFERENCES

1. Boskabadi H, Maamouri G, Mafinejad S, Rezagholizadeh F. Clinical course and prognosis of hemolytic jaundice in neonates in North East of Iran. Macedonian Journal of Medical Sciences. 2011; 4(4):403-7.

2. Ramy N, Ghany E, Alsharany W, Nada A, Darwish R, Rabie W, et al. Jaundice, phototherapy and DNA damage in full-term neonates. Journal of Perinatology. 2016; 36(2):132.

3. Sakha SH, Gharehbaghi MM, Rahbani ME. The effect of clofibrate with phototherapy in late preterm newborns with non- hemolytic jaundice. Indian J Med Sci 2009; 63: 174-79.

4. Yu C, Li H, Zhang Q, He H, Chen X, Hua Z. Report about term infants with severe hyperbilirubinemia undergoing exchange transfusion in Southwestern China during an 11-year period, from 2001 to 2011. PloS one. 2017; 12(6):e0179550.

5. Mojtabai SH, Jalali MM, Jenabi AH, Saljoughi L. Relation between indirect hyperbilirubinemia and auditory brain

response abnormality due to neonatal icter. Journal of Guilan University of Medical Sciences. 2008; 16(64):106-11.

6. Huang MJ, Kua KE, Teng HC, Tang KS, Weng HW, Huang CS. Risk factors for severe hyperbilirubinemia in neonates. Pediatr Res 2004; 56: 682-89.

7. Mohammadi Pirkashani L, Asghari G, Marofi M, Barekatain B. Effect of Chicory Extract Bath on Neonatal Bilirubin Levels: A Randomized Clinical Trial study. International Journal of Pediatrics. 2017; 5(12):6679-88.

8. Zahed Pasha Y, Ahmadpour-kacho M, Ahmadi Jazi A, Gholinia H. Effect of Probiotics on Serum Bilirubin Level in Term Neonates with Jaundice; A Randomized Clinical Trial. International Journal of Pediatrics. 2017; 5(10):5953-58.

9. Ahmadpour-kacho M, Zahed Pasha Y, Ranjbar B, Pouramir M, Hajian K, Pounasrollah M. The Effect of Oral Zinc Sulfate on Serum Bilirubine Level in Term Neonates with Jaundice. International Journal of Pediatrics. 2017; 5(6):5053-60.

10. Gourley GR. Another risk factor for neonatal hyperbilirubinemia. J Pediatr Gastroenterol Nutr 2005; 40: 388-89.

11. Sakha SH, Gharehbaghi MM. Exchange transfusion in severe hyperbilirubinemia: an experience in northwest Iran. Turk J Pediatr 2010; 52: 367-71.

12. Sgro M, Campbell D, Shah V. Incidence and causes of severe neonatal hyperbilirubinemia in Canada. CMAJ 2006; 175: 587-90.

13. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2004; 114: 297-316.

14. Maisels MJ, Bhutani VK, Bogen D, Newman TB, Stark AR, Watchko JF. Hyperbilirubinemia in the newborn infant > or = 35 weeks' gestation: an update with clarifications. Pediatrics. 2009; 124(4):1193-98.

15. Carvalho M. Treatment of neonatal hyperbilirubinemia. J Pediatr (Rio J) 2001; 77: 71-80.

16. Jackson JC. Adverse events associated with exchange transfusion in healthy and ill newborns. Pediatrics 1997; 99: E7.

17. Jaundice and hyperbilirubinemia in the newborn. In Behrman RE, Kliegman RM, Jenson HB, eds. Nelson Textbook of pediatrics. 18th ed. Philadelphia: Saunders; 2011; 603-12.

18. Michael K, Ronald JW, Ericsibley DK. Neonatal Jaundice and Liver Disease In: Martin RJ, Fanaroff AA,Walsh MC. Neonatal-Perinatal Medicine Diseases of the Fetus and Infant Medicine. 9th ed. Philadelphia: Mosby Elsevier, 2011; 1443-81.

19. Kliegman RM, Stanton BF, Schor NF, Geme JW, Behrman RE. Nelson text book of pediatrics. 19th ed. Philadelphia: Saunders; 2011: 603-12.

20. Bhat AW, Churoo BA, Iqbal Q, Sheikh MA, Iqbal J, Aziz R. Complication of exchange transfusion at a tertiary care hospital. Curr Pediatr Res 2011; 15(2): 97-9.

21. Wong RJ, Desandre GH, Sibley E, Stevenson DK. Neonatal jaundice and liver disease. In: Martin RJ, Fanaroff AA, Walsh MC (eds). Neonatal Perinatal Medicine: Disease of the Fetus and Infant (8th ed). Philadelphia: Elsevier Mosby; 2006: 1446-49.

22. Alcock GS, Liley H. Immunoglobulin infusion for isoimmune haemolytic jaundice in neonates. Cochrane Database Syst Rev 2002; 3: CD003313.

23. Porter ML, Dennis BL. Hyperbilirubinemia in the Term Newborn. Am Fam Physician 2002; 65: 599-606.

24. Avroy A. Fanaroff, Richard J. Martin. Neonatal- Perinatal medicine, diseases of the fetus and infant. 7th ed. New York: Mosby, 2002:694-97.

25. Ballot DE, Rugamba G. Exchange Transfusion for Neonatal Hyperbilirubinemia in Johannesburg, South Africa, from 2006 to 2011. International scholarly research notices. 2016 Feb 29; 2016: ID 1268149,

26. Boskabadi H, Ashrafzadeh F, Azarkish F, Khakshour A. Complications of neonatal jaundice and the predisposing factors in nNewborns. J Babol Univ Med Sci. 2015; 17(9):7-13.

27. Taheri PA, Sadeghi M, Sajjadian N. Severe neonatal hyperbilirubinemia leading to exchange transfusion. Medical journal of the Islamic Republic of Iran. 2014; 28:64.

28. Eghbalian F. Evaluation the complications of exchange transfusion in hospitalized neonates. Scientific Journal of Hamadan University of Medical Sciences. 2007; 14(2):23-7.

29. Kalkan I, Heljic S, Dzionovic A, Kurtagic S, Maksic H. Neonatal hyperbilirubinemia: evaluationand treatment. Med Arch. 1999; 53(354): 43-5.

30. Najib KS, Saki F, Hemmati F, Inaloo S. Incidence, risk factors and causes of severe neonatal hyperbilirubinemia in the South of iran (fars province). Iranian Red Crescent Medical Journal. 2013; 15(3): 260.

31. Jalali SZ, Saeidinia A, Poorabbas SM. Predictive factors of hyperbilirubinemia in newborns at University hospital in northern Iran. Indian Journal of Experimental Biology. 2017; 55: 756-60.

32. Nabavi SS, Arabhoseini A, Faridnik Y. Investigating the causes of icter leading to blood exchange in newborns born in Milad Hospital in Tehran from 1986 to 2005. Journal of Medical Council of Iran. 2010; 28(1): 36-44.

33. Hossain M, Begum M, Ahmed S, Absar MN. Causes, Management and Immediate Complications of Management of Neonatal Jaundice- A Hospital-Based Study. Journal of Enam Medical College. 2015; 5(2):104-9.

34. Shayan K, Omid F, Bayatmokhtari M, Argmand Kermani F. Some complications of blood exchange in newborns with icterus. Journal of Medival Science 2010; 2(22); 109-16.

35. Esfandiarpour B, Ebrahimi H, Karkan MF, Farahmand N, Karambin MM. Neonatal exchange transfusion for hyperbilirubinemia in Guilan (the north province of Iran): a 3-year experience. The Turkish journal of pediatrics. 2012; 54(6):626.

36. Boskabadi H, Zakerihamidi M, Bagheri F. Frequency of major and minor risk factors associated with jaundice in hospitalized newborns. Tehran University Medical Journal TUMS Publications. 2017 May 15; 75(2):141-51.

37. Boskabadi H, Maamouri G, Bagheri S. Significant neonatal weight loss related to idiopathic neonatal hyperbilirubinemia. International Journal of Pediatrics. 2014; 2(4.1): 225-31.