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Factors Associated with Exchange Transfusion among Severe Neonatal Jaundice in Malaysia

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ABSTRACT

Background: Neonatal jaundice may lead to a severe level if it is not well monitored. The long-term consequences of severe neonatal jaundice may result in devastating neurologic sequelae, including bilirubin encephalopathy and kernicterus. Exchange transfusion has remained the most effective modality for lowering serum bilirubin concentration. The present study aimed to determine the proportion and factors associated with exchange transfusion procedure among neonates with severe jaundice in Kelantan from 2015 to 2017.

Methods: This cross-sectional study was carried out among neonates with severe jaundice in Kelantan between 2015 and 2017 using jaundice surveillance data from Kelantan Health State Department.

Result: Out of the study subjects, 45 (19.7%) neonates had severe jaundice requiring an exchange transfusion procedure. From 2015 to 2017, the prevalence of severe neonatal jaundice requiring exchange transfusion raised from 17.0%-23.7%. The significant factors associated with exchange transfusion were neonatal infection, low birth weight, ABO blood group incompatibility, and maternal blood type O.

Conclusion: As evidenced by the obtained results, exchange transfusion among severe neonatal jaundice in Kelantan followed an increasing trend within the study period. Associated factors leading to exchange transfusion among severe neonatal jaundice were neonatal infection, low birth weight, ABO incompatibility, and maternal blood type O. The recognition of these factors would be of great help in developing effective strategies aimed at the prevention of exchange transfusion procedure and its subsequent complications.

Keywords: Exchange transfusion, Neonates, Severe jaundice

Introduction

Severe neonatal jaundice is a condition when the total serum bilirubin of neonates exceeds 340mmol/L (20mg/dL). This disease deserves great concern since it may lead to devastating neurological complications, such as kernicterus and acute bilirubin encephalopathy (1-3). If the bilirubin level rises continuously despite phototherapy, exchange transfusion is the choice of immediate treatment, along with intravenous immunoglobulin depending on local practices. The indications for performing exchange transfusion are based on high levels of total serum bilirubin, taking into account the risk of kernicterus and the adverse effects of the exchange transfusion intervention (4-6).

The exchange transfusion procedure is relatively safe, and all the possible fallacies may be preventable when it is conducted by expert practitioners under high careful consideration. Nonetheless, the procedure carries the risk of morbidity and mortality, either from complications or errors during the process, such as catheter-related infection, blockage of the catheter, changes in the blood flow to organs, and electrolyte imbalance (6, 7). Exchange transfusion imposes a heavy burden on health care, especially in postnatal mothers, due to increased incidence of severe neonatal jaundice, hospital admissions requirement, morbidity from complications, mortality, as well as emotional and physical exhaustion (3, 8-10).

Exchange transfusion can be prevented by an

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awareness of its contributing factors in severe neonatal jaundice since this knowledge is of great help to the surveillance system in monitoring and developing public health interventions for better provision of health care services in Malaysia. The present study aimed to determine the factors associated with exchange transfusion procedure among neonates with severe jaundice in Kelantan, Malaysia, from 2015 to 2017.

Methods

The present study was conducted based on a cross-sectional retrospective record review design within January-April 2018. Ethical approval was obtained from the Human Research and Ethics Committee (HREC), Universiti Sains, Malaysia, and Medical Research and Ethics Committee, Ministry of Health, Malaysia.

The hyperbilirubinemia level was evaluated using umbilical cord, venous, or capillary serum of neonates. All neonates with severe hyperbilirubinemia, those with total serum bilirubin level more than 340mmol/L (20mg/dL), in all government and private clinics and hospitals in Kelantan, Malaysia, between January 2015 and December 2017 were included in the data pool. The comprehensive data were acquired from the notification of cases with severe neonatal jaundice, MMN/NNJ form (Monitoring and Management Neonatal/Neonatal Jaundice), a form used for severe neonatal jaundice surveillance in Malaysia. We excluded those with congenital anomalies and inborn errors of metabolism. The following data were collected using detailed proforma.

The data were analyzed in SPSS software (version 24.0). Multiple logistic regression analysis was used to define significant associated factors of outcome variables. Prior to logistic regression analysis, a univariate analysis was performed using the logistic regression analysis to evaluate the association between each independent variable and the outcome variables. Variables with P<0.25 following univariate analysis were included in the multiple logistic models.

Results

Characteristics of severe neonatal jaundice cases undergoing exchange transfusion

During this three-year study period, 233 neonates were admitted for severe hyperbilirubinemia. Out of these cases, 228 neonates met the inclusion criteria. Five neonates were excluded from the study due to congenital abnormalities. No neonates with the inborn error of metabolism were reported. A total of 45 exchange transfusion procedures were accomplished which encompassed almost one-fifth of severe neonatal jaundice cases (19.7%), while other 183 (80.3%) neonates only underwent intensive phototherapy. The majority of mothers of neonates with severe jaundice were within the age range of 17-49 years, multiparous (62.2%), and delivered in the government hospital (91.1%) (Table 1).

Factors associated with exchange transfusion among severe neonatal jaundice

As illustrated in Table 2, the significant associated factors with exchange transfusion among severe neonatal jaundice were maternal blood type of O, ABO incompatibility, low birth weight, infection in newborn, the age of mother, hospital delivery, preterm birth, and Glucose-6-phosphate dehydrogenase deficiency (G6PD) deficiency. Other factors, such as the number of parities, birth trauma, and inadequate breastfeeding, were found insignificant.

The results of multiple logistic regression demonstrated that the significant factors contributing to the exchange transfusion procedure

Table 1. Characteristics of severe neonatal jaundice cases undergoing exchange transfusion in Kelantan 2015-2017 (n=228)

Characteristic	n (%)	Mean (SD)
Maternal age (years)		31.4 (5.87)
Parity		
Primiparity	17 (37.8)	
Multipara	28 (62.2)	
Place of Delivery		
Government Hospital	41 (91.1)	
Non-Government Hospital	4 (8.9)	
Day of detection (days)		3.8 (1.80)
Highest total serum bilirubin detected (mmol/dL)		439.1 (51.02)

were maternal blood type O, ABO incompatibility, low birth weight, and infection of neonates as illustrated in Table 3. The odds of having a neonate with severe jaundice undergoing exchange transfusion are 2.65 times higher in mothers with blood type O, compared to their counterparts with other blood types (95% CI: 1.27; 5.53; P=0.009). Moreover, the odds of severe jaundice requiring exchange transfusion are 3.71 times higher in neonates with ABO incompatibility, compared to those without ABO incompatibility (95% CI: 1.43,9.61; p= 0.007). Moreover, the odds of this disease are 3.55 times higher in neonates with low birth weight, compared to those with normal weight (95% CI: 1.56, 8.06; p=0.002). Finally, neonates with infection are 6.42 times more likely to undergo exchange transfusion, compared to those without infection (95% CI: 2.14, 19.20; p= 0.001).

There was no multicollinearity problem among the independent variables. The Hosmer–Lemeshow test for the fitness of the final model was not significant (P=0.408), pointing to the fitness of this model. The fitness of this model was also supported by the classification table and receiver operating characteristics (ROC) curve. The classification table demonstrated that the overall percentage was 82.5%, and the area under the curve was 0.744. Finally, this model can accurately discriminate 74.4% of the cases.

Table 2. Factors associated with neonatal jaundice requiring exchange transfusion in Kelantan 2015-2017 (n=228).

Variables	Crude OR (95%CI)	Wald statistic (df)	P-value*
Maternal age (years)	1.046 (0.990, 1.104)	2.582 (1)	0.108
Number of parities			
>1 parity	1		
Primiparity	1.076 (0.549, 2.112)	0.046 (1)	0.831
Place of delivery			
Non-Hospital	1		
Hospital	2.453 (0.686, 8.775)	1.904 (1)	0.168
Blood group O			
No	1		
Yes	2.668 (1.331, 5.345)	7.658 (1)	0.006
ABO incompatibility			
No	1		
Yes	3.200 (1.328, 7.708)	6.725 (1)	0.010
Preterm birth			
No	1		
Yes	1.929 (0.816, 4.559)	2.239 (1)	0.135
Birth weight (grams)			
≥2500grams	1		
<2500grams	2.500 (1.183, 5.285)	5.756 (1)	0.016
Infections of newborn			
No	1		
Yes	3.741 (1.383, 10.119)	6.751 (1)	0.009
Birth trauma			
No	1		
Yes	0.809 (0.092, 7.102)	0.037 (1)	0.848
G6PD deficiency			
No	1		
Yes	0.469 (0.135, 1.631)	1.419 (1)	0.234
Inadequate breastfeeding			
No	1		
Yes	0.951 (0.462,1.956)	0.019 (1)	0.891

*Simple logistic regression

Table 3. Multiple logistic regression analysis of factors associated with neonatal jaundice requiring exchange transfusion in Kelantan 2015-2017 (n=228)

Variables	B	Adjusted OR (95%CI)	P-value*
Maternal blood group O			
No	1		
Yes	1.0975	2.651 (1.270, 5.534)	0.009
ABO incompatibility			
No	1		
Yes	1.312	3.714 (1.435, 9.611)	0.007
Birth weight (grams)			
≥2500grams	1		
<2500grams	1.268	3.552 (1.564, 8.065)	0.002
Infections of neonates			
No	1		
Yes	1.860	6.423 (2.148, 19.205)	0.001

Constant = -2.649
Backward LR method was applied
No multicollinerity and no interaction
Hosmer Lemeshow test, p-value=0.408
Classification table 82.5% correctly classified
ROC (Area under the curve) is 0.744
The model can accurately discriminate 74.4% of the cases

Discussion

As evidenced by the obtained results, maternal blood type O and ABO incompatibility were significant factors associated with severe hyperbilirubinemia requiring exchange transfusion. This finding is in line with the results of an Indian study on severe neonatal jaundice requiring an exchange transfusion procedure (11). Maternal blood type O has been related to ABO incompatibility in some studies which pointed to the reaction of maternal alloimmunization to fetal antigens and IgG antibodies that can pass through the placenta and cause hemolytic events in offspring with A or B blood types (12-15).

According to Arnolda, infection is one of the significant factors of exchange transfusion procedure among neonates with severe jaundice (16). It has been pointed out that infection can increase the risk of severe jaundice to bilirubin neurotoxicity level by changing the attached affinity of albumin; subsequently, facilitating bilirubin penetration into the blood-brain barrier. During that phase, the process of bilirubin conjugation is inhibited by the existence of sepsis (17). Jaundice in septic neonates is also thought to be a consequence of rapid hemolysis. Neonatal erythrocytes are susceptible to cell injury in response to oxidative stress. In addition, heme oxygenase is induced by oxidants, leading to increased catabolism of heme to bilirubin. Intrauterine infections may cause giant cell hepatitis and jaundice anytime during the neonatal period (3, 11, 18).

Furthermore, birth weight plays a crucial role in exchange transfusion, as observed in the present study where 68.9% of neonates with severe jaundice had low birth weight. This finding is in accordance with those obtained by Owa and Ogunlesi (18) who reported that 44.4% of neonates with severe jaundice requiring exchange transfusion had low birth weight. Menon (19) reported that low birth weight was a main neonatal determinant with a very strong association with 80.65% of neonates with severe jaundice who had 24.54 times the odds of undergoing exchange transfusion, compared to their counterparts with normal birth weight. Low birth weight neonates are more likely to face subsequent problems, such as asphyxia, hypoglycemia, hypothermia, and acidosis, all of which contribute to the development of severe jaundice (20).

Some other variables, including hospital delivery, preterm birth, and G6PD deficiency, were taken into account in adjusting for confounding effects; nonetheless, the result indicated that they were insignificant. Hospital delivery was found to be an important factor in several studies, especially in lower-middle-income countries (11, 21, 22); however, it was insignificant in the current study. Out-of-hospital delivery is associated with delayed identification of jaundice often culminating in a late presentation at the hospital where appropriate care is available (23).

Prematurity was not detected as one of the associated factors for severe neonatal jaundice requiring an exchange blood transfusion procedure. This finding differs from other studies which pointed out that prematurity was a major determinant for neonatal jaundice requiring exchange blood transfusion procedure (6, 10, 24). Premature neonates have higher serum bilirubin levels for a longer time due to hepatic immaturity; moreover, there is delayed lactogenesis in their mothers (19, 23)

The G6PD deficiency was also found insignificant in the present study, accounting for only 8.89% of all causes of exchange blood transfusion. This result is lower than the prevalence of G6PD deficiency in term neonates undergoing exchange blood transfusion in Iran reported as 14% (13) and 19% (25) of the study population. A study performed by Esfandiarpour et al. (2012) found that the high prevalence of G6PD deficiency could be due to the variety of races (26). The prevalence of G6PD deficiency in Turkey is high in relation to the geographic location and ethnicity (27), as compared to the present study in which the majority of participants were Malays.

All of these significant variables that were discussed can be classified as modifiable and non-modifiable factors. The identified significant modifiable factors were infections and low birth weight of neonates, while ABO incompatibility and maternal blood type O were significant non-modifiable factors. The recognition of these significant associated modifiable factors is of great help to the reduction of the cases of severe neonatal jaundice and exchange transfusion.

Limitations and strengths

Among the notable limitations of the present study, we can refer to dependency on secondary data, self-reporting nature of data collection, absence of long-term follow-up data on the neonates, as well as the unknown rate of neurodevelopmental problems from severe hyperbilirubinemia and adverse event of exchange transfusion.

Conclusion

Jaundice in neonates may lead to a worsening of symptoms and severe jaundice if it is not well monitored. The long-standing results of severe neonatal jaundice may result in devastating neurologic sequelae, including bilirubin encephalopathy and kernicterus. Exchange transfusion has remained the most expeditious intervention for lowering serum bilirubin concentration. In the current study, the major determinants of neonatal jaundice requiring exchange transfusion were ABO incompatibility, maternal blood type O, as well as neonatal infections and low birth weight (<2500grams).

The recognition of these associated factors is of great help to raise awareness of major determinants, especially modifiable factors that can be included in the program, such as infection and low birth weight of neonates. Infection was the most prevalent risk factor for severe hyperbilirubinemia. Therefore, all neonates with suspected symptoms of infection, such as poor sucking reflex, feverish body, and lethargy, must be alerted to possible severe jaundice problems and advised of the necessity of medical attention. The second prevalent associated factor was low birth weight; accordingly, it is recommended to follow necessary protocols for the prevention of low birth weight.

The findings of the present study would be of great help in formulating effective strategies and policy initiatives to identify high-risk cases. Furthermore, they can shed light on the optimization of management strategies aimed at reducing the incidence of neonatal jaundice, especially an awareness of modifiable associated factors, as well as the complications and adverse effects of the exchange transfusion procedure.

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Conflicts of interest

The authors declare that they have no conflict of interest regarding the publication of the present study.

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