Original Article

Exchange Transfusion Trends and Risk Factors for Extreme Neonatal Hyperbilirubinemia over 10 Years in Shiraz, Iran

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Received: 20 June 2023
Revised: 14 August 2023
Accepted: 28 September 2023

Abstract

Background: Exchange transfusion (ET) is an effective treatment for acute bilirubin encephalopathy and extreme neonatal hyperbilirubinemia (ENH). It can reduce mortality and morbidity. This study aimed to investigate the trends and risk factors of ENH requiring ET in hospitalized neonates in Iran.

Methods: A retrospective analysis of medical records of neonates who underwent ET due to ENH was conducted from 2011 to 2021, in Shiraz, Iran. Clinical records were used to gather demographic and laboratory data. The quantitative data were expressed as mean±SD, and qualitative data was presented as frequency and percentage. $P<0.05$ was considered statistically significant.

Results: During the study, 377 ETs were performed for 329 patients. The annual rate of ET decreased by 71.2% during the study period. The most common risk factor of ENH was glucose-6-phosphate dehydrogenase (G6PD) deficiency (35%), followed by prematurity (13.06%), ABO hemolytic disease (7.6%), sepsis (6.4%), Rh hemolytic disease (6.08%), and minor blood group incompatibility (3.34%). In 28.52% of the cases, the cause of ENH was not identified. 17 (5.1%) neonates had acute bilirubin encephalopathy, of whom 6 (35.29%) had G6PD deficiency, 6 (35.29%) had ABO incompatibility, and 2 (11.76%) had Rh incompatibility.

Conclusion: Although the rate of ET occurrence has decreased, it seems necessary to consider different risk factors and appropriate guidelines for early identification and management of neonates at risk of ENH should be developed. The findings of the study highlighted the important risk factors of ENH in southern Iran, allowing for the development of appropriate prevention strategies.

Please cite this article as: Hemmati F, Mahini SM, Bushehri M, Asadi AH, Barzegar H. Exchange Transfusion Trends and Risk Factors for Extreme Neonatal Hyperbilirubinemia over 10 Years in Shiraz, Iran. Iran J Med Sci. doi: 10.30476/ijms.2023.99176.3123.

Keywords ● Hyperbilirubinemia ● Neonatal ● Jaundice ● Kernicterus ● Risk factors

What's Known

- Extreme hyperbilirubinemia is a major concern. Despite its decline throughout the years, it remains an important cause of mortality and morbidity in neonates.

What's New

- G6PD deficiency is the most prevalent risk factor of extreme newborn hyperbilirubinemia that leads to exchange transfusion in southern Iran. Therefore, hyperbilirubinemia must be monitored closely in these infants. Moreover, screening for G6PD deficiency is essential.

Introduction

Hyperbilirubinemia is a common and challenging condition in neonates that affects approximately 50% of term and 80% of preterm newborns.[1] It is a prevalent cause of hospital readmission in the first week of life.[2] Hyperbilirubinemia is frequently benign. However, it can be harmful and cause

In the present study, ABO incompatibility with hemolysis was the third risk factor that led to ET, while it was the most common cause of ABE or ENH reported in the United States, Canada, China, and Nigeria, affecting 19-55% of infants.[30-33] About 25.5% of the patients were ABO incompatible. ABO incompatibility is defined as the situation in which infants with blood group A or B are born to mothers with group O because anti-B or anti-A antibodies of blood group-O mothers are predominantly smaller IgG molecules that may cross the placenta, as opposed to the corresponding antibodies of blood groups A or B mothers, which are IgM molecules with limited ability to cross the placenta. Some or all of the following criteria are required to support the diagnosis of ABO hemolytic disease: hyperbilirubinemia on the first day of life, anemia, spherocytosis increased reticulocyte counts, and increased end-tidal CO measurements corrected for ambient CO (ETCOc). We did not assess. However, according to other criteria, 25 (7.6%) cases with ENH had ABO hemolytic disease. In ABO-incompatible newborns with negative DAT, a polymorphism for the (TA) 7 sequence in the promoter of the gene encoding UGT1A1 significantly increased the incidence of hyperbilirubinemia.[29] In Fars Province, the prevalence of Gilbert syndrome, detected using the rifampin test, was 25.6% and 12.8% in males and females, respectively.[34] Thus, ABO incompatibility might have increased the risk of ENH in our neonatal population, who had the Gilbert syndrome gene.

Sepsis occurred in 6.4% of neonates with ENH and 29.4% of patients with ABE. Sepsis causes hyperbilirubinemia through a variety of mechanisms, including hemolysis, impaired conjugation, and decreased bilirubin excretion. Neonatal RBCs are susceptible to injury due to oxidative stress, and sepsis-induced disseminated intravascular coagulation can lead to hemolysis.[35] Furthermore, oxidants can stimulate the heme oxygenase enzyme, resulting in enhanced heme catabolism to bilirubin. In addition, sepsis-induced hepatitis can cause conjugated hyperbilirubinemia. Acidosis and meningitis, which might be associated with sepsis, enhanced the risk of ABE with lower TSB levels.[36, 37] In the studied patients, sepsis was not the primary risk factor. However, it played a significant role in the increased incidence of ABE.

11 (3.34%) of our cases were classified as minor blood group incompatibility due to positive DCT in the absence of ABO and Rh incompatibility. The most reported RBC antibodies that cause hemolytic disease in the newborn were anti-C, anti-Kell, and anti-E.[38, 39]

The advantages of the present study were enrolling a large number of participants and considering the criteria for ABO hemolytic disease, which were overlooked in previous studies and might explain the reason for more prevalent ABO incompatibility in their results. The limitation of this study was its retrospective nature. Since the data were collected from medical records, some details were not documented, resulting in incomplete data. Furthermore, we did not have ETCOc and albumin levels, which could help in determining the pathogenesis of ENH and susceptibility to ABE, respectively. Pediatricians and other healthcare providers should be educated on the causes, prevention, and diagnosis of ENH. Therefore, further prospective studies with more detailed evaluation such as the determination of minor blood group antibodies, ETCOc, and albumin levels are recommended. Moreover, a follow-up study of patients who have undergone ET should also be considered.

Conclusion

Extreme hyperbilirubinemia is a serious neonatal health issue, and finding the risk factors of ENH in each region is crucial for developing prevention strategies. The annual rate of ET has decreased during the last decade. However, ABE and kernicterus should be eliminated while the rate of ET should be reduced as much as possible. This study highlights the key risk factors of ENH in southern Iran.

G6PD deficiency was the most common cause of ENH, and the prevalence of G6PD deficiency in ENH and ABE suggested a cause-and-effect relationship between them. Consequently, the screening program for G6PD in Iran seems feasible. Late prematurity was the second risk factor, and appropriate management of preterm neonates was crucial for preventing ENH. ABO hemolytic disease, Rh hemolytic disease, minor blood group incompatibility, and sepsis were other etiologies of ET in neonates which required appropriate preventative strategies.

Acknowledgment

The authors would like to thank Shiraz University of Medical Sciences (Shiraz, Iran), as well as the Center for Development of Clinical Research of Namazi Hospital, and Dr. Nasrin Shokrpour for editorial assistance.

Authors' Contribution

FH and HB: Concept and design. SMM, MB,