Original Article

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Quick Response Code:

Website: www.jehp.net
DOI: 10.4103/jehp.jehp_895_23

Developmental outcome of neonates underwent exchange transfusion due to hyperbilirubinemia: A single-center experience

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Abstract:

BACKGROUND: Exchange transfusion due to hyperbilirubinemia is performed in neonates with signs of encephalopathy or if the level of bilirubin is more than the exchange threshold and not responding to intensive phototherapy. Bilirubin passage through the blood–brain barrier can cause injury to different sites of the brain and may have long-life effects. In this study, we aimed to evaluate the neonates who underwent exchange transfusion and investigated their developmental problems. By recognizing their developmental delay, we can recommend screening time and early occupational therapy if needed.

METHODS AND MATERIAL: This is a retrospective study on neonates who underwent exchange transfusion due to hyperbilirubinemia in Namazi and Hafez hospitals, in Shiraz, Iran, between 2016 and 2021. The exclusion criteria were the unwillingness of the parents to participate in the study or incomplete data. Children who died were also excluded from the study. Demographic and clinical data were obtained from hospital records. Children were invited to the clinic for examination, and development was assessed by Ages and Stages Questionnaires (ASQ). All neonates had done auditory brainstem response. The result was obtained. Quantitative data are reported as mean standard deviation (SD) and qualitative data with frequency and percentage. Spearman's correlation coefficient and Chi-square test were used, and the *P* value was significant below 0.05.

RESULTS: Eighty-seven neonates were enrolled. Forty-nine (56.3%) were female, and 38 (43.7%) were male. Glucose-6-phosphate dehydrogenase(G6PD) deficiency was the most prevalent hematologic cause of hyperbilirubinemia (23%). Auditory disorder, speech disorder, motor disorder, and encephalopathy were seen in four (4.6%), two (2.3%), three (3.4%), and four infants (4.6%), respectively.

CONCLUSION: Bilirubin neurotoxicity can cause developmental impairment including auditory, speech, and motor disorders besides encephalopathy. Early recognition and proper early intervention can lead to better outcomes for the child, family, and society.

Keywords:

Development, disorder, exchange transfusion, hyperbilirubinemia

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Received: 24-06-2023
Accepted: 23-07-2023
Published: 11-07-2024

Introduction

Bilirubin neurotoxicity is a major concern in the neonatology field as hyperbilirubinemia is the most common problem during infancy. It occurs when the total bilirubin level reaches more than the ability of neuroprotective defenses.[1] Neuroinflammation—release of inflammatory mediators and immune response—plays a role in brain injury and the neurodevelopment of neonates with severe hyperbilirubinemia.[2] Bilirubin injury mostly affects the basal ganglia, brain stem, hippocampus, and cerebellum.[3]

How to cite this article: Najib KS, Ostovar L, Rezaei M, Barzegar H. Developmental outcome of neonates underwent exchange transfusion due to hyperbilirubinemia: A single-center experience. J Edu Health Promot 2024;13:209.

Chronic bilirubin encephalopathy is mainly known as kernicterus and is characterized by motor and auditory disabilities. Subtle mental effects, attention deficit disorder, and autism can also occur in bilirubin neurotoxicity.[4-6] Exchange transfusion, an invasive procedure, is the treatment of choice to prevent bilirubin neurotoxicity by rapid elimination of bilirubin.[7] We should assess the potential risk and errors related to this procedure to reduce the complications and achieve a safe healthcare system.[8] Despite protective strategies and treatment guidelines for hyperbilirubinemia, bilirubin neurotoxicity is seen. It can affect the long life of the individual, family, and society. Thus, it is important to recognize epidemiology. According to a review by Riordan *et al*.,[9] kernicterus is now understood to be a spectrum of severity and phenotypes known as kernicterus spectrum disorder, and genetic factors may contribute to the susceptibility to bilirubin neurotoxicity. In some developing countries, the incidence of severe neonatal jaundice and kernicterus is much higher than in developed regions, due to various medical and environmental factors.[3,10,11]

It is important to recognize developmental delay because it can interfere with children's learning, growth, and well-being. Early intervention services can help children to catch up with their peers and reach their full potential. In this study, we aimed to evaluate the development and hearing of patients who underwent exchange transfusion during infancy.

Materials and Methods

Study design and setting

This retrospective cross-sectional study was conducted on neonates admitted to the neonatal intensive care units in Namazi and Hafez hospitals, Shiraz, Iran, between 2016 and 2021, who underwent exchange transfusion for severe hyperbilirubinemia.

Study participants and sampling

The inclusion criteria encompassed neonates with bilirubin encephalopathy or bilirubin levels exceeding the threshold for exchange transfusion in accordance with the guideline adopted by the American Academy of Pediatrics.[12] The exclusion criteria were the disinclination of parents to assist the study or incomplete data, the presence of asphyxia (Apgar score <7 in 5 min, cord blood gas potential of hydrogen (PH) <7, or base excess (BE) <-12), and major systemic or congenital diseases such as congenital heart disease. Children who died were also excluded from the study.

Data collection tool and technique

Demographic and clinical data including age, sex, family history, gestational age (GA), type of delivery, birth weight (BW), maternal age, feeding, status of bilirubin, etiology of hyperbilirubinemia, and signs and symptoms on admission were obtained from their medical records. Children who had undergone exchange transfusion were invited to a clinic through a call to action, where they underwent an examination. Parents were interviewed regarding the child's medical history and treatment progress, and subsequently, the children were assessed using an age-appropriate questionnaire, Ages and Stages Questionnaires (ASQ), to evaluate their developmental status. This questionnaire covers developmental assessment from two months to 60 months of age. It includes communication, gross motor, fine motor, problem-solving, and personal social based on age. Each domain consists of six items that parents rate as yes (10 points), sometimes (5 points), or not yet (0 points). The total score for each domain ranges from 0 to 60. The total scores are compared to the cutoff scores to determine whether the child's development is on track, needs monitoring, or requires further evaluation.[13] ASQ demonstrates good reliability and validity. The questionnaire shows high internal consistency with a reliability coefficient (alpha) of 0.97. The correlation coefficients between the latent variables are significant, indicating moderate to large association. The intraclass correlation coefficient between the two ASQ administrations is 0.94, indicating good reliability. In terms of validity, the ASQ scores are significantly correlated with the intended constructs, suggesting that the questionnaire effectively measures developmental milestones. The Kaiser–Meyer–Olkin measure supports the validity of the ASQ. Overall, these findings affirm the reliability and validity of the ASQ for assessing developmental outcomes in children.[14] The reliability and validity of the Persian questionnaire are confirmed in Iran.[15]

After the parents filled out the questionnaire, a pediatric neurologist examined the neonates suspected of neurologic developmental delay. The results were divided using a 5-point scale: 1. a completely normal condition, 2. normal or suspicious results, 3. abnormal results with mild disability, 4. abnormal results with moderate disability, and 5. abnormal results with severe disability. The neurologist visited suspicious or abnormal patients and also patients who were under speech therapy or any occupational therapy. Considering the importance of respecting patients' rights,[16] all stages of history taking, examination, and evaluation for each patient were done with respect for privacy.

All participants had done auditory brainstem response (ABR) in infancy after discharge from the hospital. All of them had been advised for hearing screening and ABR after discharge from the hospital, and they had done it at most on 3 months old. The results

were also obtained from parents. All data were analyzed using statistical package for the social sciences (SPSS) ver. 21. Descriptive results are presented as standard deviations of the average with confidence limits or a 95% ratio, and qualitative data are presented as percentages. The Kolmogorov–Smirnov test was used to check the normal distribution of quantitative data. We also used Spearman's correlation coefficient and Chi-square test. In conducted tests, the significance level was below 0.05.

Ethical consideration

All methods were performed in accordance with the relevant guidelines and regulations. Informed consent was obtained from parents. This article is extracted from the residency thesis by Leila Ostovar at Shiraz University of Medical Sciences. The Medical Ethics Committee approved the study protocol of Shiraz University of Medical Sciences (Ethics Code: IR.SUMS.MED.REC.1401.111).

Results

In this retrospective study, a total of 87 neonates were enrolled. Among them, 78 (89.7%) neonates were term, and nine (10.3%) were preterm. Of all neonates, 49 (56.3%) were female and 38 (43.7%) were male. The majority of births occurred through vaginal delivery (72.4%), while 27.6% were delivered via cesarean section. Maternal age ranged from 19 to 37 years with a mean age of 27.78 ± 4.58 years. The neonates' weights ranged from 1600 grams to 4000 grams, with a mean weight of 2959.60 ± 495.59. The maximum total bilirubin level observed was 55 mg/dl, while the minimum was 12 mg/dl with a mean of 27.18 ± 7.04.

The frequency of G6PD deficiency, ABO incompatibility, Rhesus (Rh) isoimmunization, and sepsis among the neonates was 23%, 16.1%, 9.2%, and 8%, respectively [Figure 1].

The association of auditory disorder, speech disorder, motor disorder, and encephalopathy with bilirubin level, type of delivery, birth weight, and GA is shown in Table 1.

The auditory disorders were observed in four (4.6%) participants, with two being term infants and two being preterm infants. There was a statistically significant association between auditory disorders and GA and total bilirubin levels (*P* value 0.008 and 0.027, respectively). Two infants were diagnosed with speech disorders, with one being term and the other being preterm. However, there was no statistically significant association between speech disorders and GA (*P* value 0.062). Motor disorders were identified in three (3.4%) infants, with two being term and one being preterm.

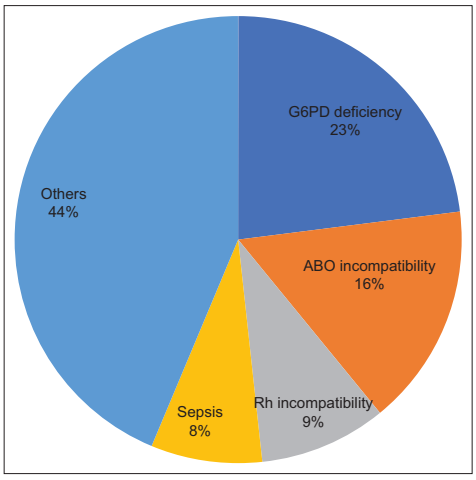

Figure 1: Etiologies of hyperbilirubinemia

Table 1: Association between GA, BW, type of delivery and bilirubin level, and outcomes of neonates who underwent exchange transfusion

Outcome	Frequency (%)	Bilirubin level¶	Type of delivery¶¶	BW¶	GA¶¶
Auditory disorder	4 (4.6%)	0.027*	0.206	0.444	0.008*
Speech disorder	2 (2.3%)	0.038*	0.377	0.955	0.062
Motor disorder	3 (3.4%)	0.686	0.277	0.881	0.183
Encephalopathy	4 (4.6%)	0.526	0.206	0.920	0.324

**P* is significant below 0.05. ¶Assessed by Spearman's correlation coefficient. ¶¶Assessed by the Chi-square test

Encephalopathy was observed in four (4.6%) neonates with three being term infants and one being preterm. However, there was no statistically significant association between encephalopathy and GA, BW, type of delivery, or total bilirubin status. Among the neonates born via vaginal delivery (n = 63), four developed encephalopathy, four had auditory disorders, two had speech disorders, and three had motor disorders as a result of severe hyperbilirubinemia. None of the neonates born via cesarean section developed any disability or encephalopathy. Nevertheless, there was no statistically significant association between the type of delivery and the consequences of hyperbilirubinemia (*P* value > 0.05). Similarly, there was no statistically significant association between birth weight and hyperbilirubinemia-induced neurologic disorders.

Discussion

Hyperbilirubinemia is a common clinical condition in the neonatal period.[17] Although it seems benign, it has severe manifestations and sequelae such as bilirubin neurotoxicity. In our study, we aimed to investigate the developmental outcomes of neonates who underwent exchange transfusion due to severe hyperbilirubinemia. Comparing our findings with previous studies, we observed similar trends in the incidence of developmental disabilities. Arpit *et al*.[18] reported that 25.7% of

their cohort (n = 35) had developmental disabilities at 6 months old, and at 12 months old, 12.5% of the remaining neonates exhibited developmental delay. Similarly, Gharehbeigi *et al*.[19] found that of 90 neonates with severe hyperbilirubinemia, 11 (12.2%) had low scores in their developmental evaluation. Zhang *et al*.[20] in a larger cohort of 462 neonates who underwent exchange transfusion reported a poor outcome in 13.9% of cases. In our study, we found that 13 (14.9%) of neonates had developmental disabilities. These findings support the importance of monitoring and assessing the developmental outcomes of neonates with severe hyperbilirubinemia.

Rh incompatibility, ABO incompatibility, and G6PD are hematologic etiologies of hyperbilirubinemia.[17] In a systematic review by Boskabadi *et al*.,[21] ABO incompatibility was the most common etiology of hyperbilirubinemia. Babaei *et al*.[22] reported ABO incompatibility as the most common hematologic etiology of severe hyperbilirubinemia in neonates who underwent exchange transfusion. In our previous study on 1134 neonates with hyperbilirubinemia, G6PD was the most prevalent deficiency.[23] In this study, among neonates with severe hyperbilirubinemia and exchange transfusion, G6PD, with a prevalence of 23%, was the most frequent deficiency. The prevalence of G6PD deficiency is 5.5% in Iran,[24] and G6PD screening is done in the neonatal period. G6PD deficiency plays a role in neurotoxicity by hemolysis and increasing bilirubin. The buffering capacity against bilirubin-induced reactive oxygen species is also reduced.[25,26] Kuzniewicz MW *et al*.[27] reported G6PD deficiency as a leading cause of severe hazardous hyperbilirubinemia among neonates with identified etiology.

In the present study, we observed an auditory disorder in 4.6% of neonates, and there was a statistically significant association between auditory disorder and total bilirubin (*P* value 0.027). The higher levels of bilirubin were associated with an increased risk of hearing impairment. Elevated bilirubin levels can lead to auditory dysfunction and permanent damage to the auditory system. Studies have shown that the risk of abnormal ABR is higher when the total bilirubin level exceeds 20 mg/dl compared with levels below 20 mg/dl.[28] In a study by ElTatawy *et al*.,[4] a positive and significant association was found between the total bilirubin levels and abnormal ABR results. The reported rates of auditory neuropathy spectrum disorder among neonates who underwent exchange transfusion in other studies were 11.57%,[29] 15%,[30] and 12.39%.[29] The exact mechanism of auditory impairment in hyperbilirubinemia is not well known; the possible causes are the destruction of the specific calcium buffer system in the auditory nuclei by bilirubin and the destruction of calmodulin-dependent kinase 2 function by bilirubin, which is an essential enzyme for neuronal function.[31]

In this study, among 87 neonates, we found that two individuals (2.3%) exhibited speech disorders during the follow-up period. We did not observe a significant association between the presence of speech disorders and GA. In contrast to our result, Maimburg *et al*.[32] demonstrated that term neonates with hyperbilirubinemia had an increased risk for speech and language disorders, while preterm ones were not statistically significant at risk. Auditory and language disorders can develop in affected children together as they suffer auditory deprivation in a critical period of learning a language.[33] Hokkanen *et al*.[34] reported 9% speech disorder in their 30 years of follow-up of adults who had neonatal hyperbilirubinemia.

Among all participants, 3.4% exhibited motor disorders, two were term infants, and one was a preterm infant. Our findings aligned with the hypothesis that term infants are more likely to develop motor disorders, whereas preterm infants are more prone to auditory disorders.[35] Bilirubin-induced injury to the globus pallidus, subthalamic nuclei, cerebellum, and brainstem is known to contribute to the development of movement disorders.[35] Kernicterus, a severe manifestation of bilirubin toxicity, is characterized by dystonia and choreoathetosis, with the upper extremities more severely affected.[36] Medications that stimulate ɤ-aminobutyric acid type b (GABA-B) and anticholinergic drugs,[31] physiotherapy,[37] and massage therapy[38] can improve the motor disorders of these patients.

Bilirubin encephalopathy was observed in 4.6% of the neonates, predominantly in term infants. Although we did not find a statistically significant association between the bilirubin level and the development of encephalopathy, a study by Ding *et al*.[39] reported a significant association. In their study of 46 newborns who underwent exchange transfusion for severe hyperbilirubinemia, they demonstrated a statistically significant association between indirect bilirubin levels and the development of encephalopathy. The results of a study conducted in Egypt showed an incidence of 12% for acute bilirubin encephalopathy among patients admitted with hyperbilirubinemia, and just 12.4% of them had a severe form.[40]

In this study, we examined the association between GA and BW with the developmental outcomes of neonates. We found that auditory disorders had a significant association with GA. However, we did not find a significant association between any of the outcomes and BW.

The present study has several strengths that contribute to its scientific value. One of the strengths is the long-term follow-up of infants, which provides valuable insights into their developmental outcomes following exchange transfusion. Another one was the inclusion of a pediatric neurologist in the assessment of developmental outcomes. The neurologist employed standardized neurodevelopmental assessments, which are widely recognized and accepted in the field, ensuring the reliability of the findings. Furthermore, the use of an age-appropriate ASQ questionnaire enabled us to gather detailed and objective information about the infant's developmental milestones and identify any potential delays or disabilities.

Limitation and recommendation

Some limitations should be acknowledged. Firstly, our study did not explore other potential contributing factors to the developmental outcomes, such as specific medications administered, length of hospital stay, and concurrent illnesses. These factors could have influenced the developmental trajectory of neonates and should be considered in future research. Another limitation is the relatively small sample size, which may have limited the generalizability of the findings. To obtain more robust and representative results, future studies should aim for larger sample sizes and include a more diverse population.

In addition, it is essential to determine the optimal timing for auditory and developmental screening in future studies. Identifying the most appropriate age for screening and auditory assessments can contribute to the early detection and intervention of potential issues. By establishing specific guidelines for screening protocols, healthcare professionals can ensure timely and accurate identification of developmental and auditory impairments in neonates who underwent exchange transfusion.

Conclusion

In conclusion, our study highlights the potential long-term consequences of neonatal hyperbilirubinemia on individuals, their families, and society as a whole. The neurotoxicity associated with high levels of bilirubin can result in developmental and auditory impairments that can significantly impact the quality of life. Our study revealed that 14.9% of neonates who underwent exchange transfusion exhibited developmental or auditory difficulties. Further studies are needed to investigate the prevalence of developmental problems related to extreme hyperbilirubinemia and its long-term effects. More research should be conducted to find early interventions that would reduce these complications.

Acknowledgement

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

Ethical statement

The Medical Ethics Committee approved the study protocol of Shiraz University of Medical Sciences (Ethics Code: IR.SUMS.MED.REC.1401.111).

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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