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Original Research Article

Assessment and Connection to the Neurologic Outcome of Severe Hyperbilirubinemia in Term Infants

Renu Bharati[1], Sweety Rani[2]

[1]Junior Resident, Department of Pediatrics, Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar, India

[2]Senior Resident, Department of Obstetrics and Gynecology, Indira Gandhi Institute of Medical Sciences, Sheikhpura, Patna, Bihar, India

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Corresponding author: Dr. Sweety Rani
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Abstract

Aim: Evaluation of risk factors for severe hyperbilirubinemia and its relationship with neurological outcome in term infant. **Methods:** This prospective observational study was conducted Department of Pediatrics, Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar, India for 1 year. All consecutive neonates more than 35 weeks of gestation admitted in the NICU with a serum bilirubin >20 mg % in first 72 h of life or >25 mg% after first 72 h formed the study subjects. **Results:** A total of 80 neonates were enrolled. Both the study groups were comparable with respect to age (125.21±77.85h vs 135.54±75.19 h; p = 0.63), sex (male/female 2.1:1 vs 1.39:1; p = 0.74), presence of SGA babies (4[13.33%] vs 4 [8%]; p = 1.22), socioeconomic status (p = 0.48), and antenatal care (p = 1.2). However, neonates with ABE weighed less on admission than those without ABE (2324.87±429.69 g vs 2531.87±382.91 g; p = 0.027) and the causes of hyperbilirubinemia (p = 0.033) were significantly different of 30 neonates with ABE, 19 presented in stage II and 11 presented in stages III of ABE. Table 2 shows the risk factors associated with development of ABE. A lower weight on admission (2331.886 397 g vs 2511.87 379g; p = 0.023), ABO/Rh incompatibility (odds ratio 4.20; 95% CI: 1.23–14, p = 0.037), a positive Coomb's test (odds ratio 6.1; 95% CI: 1.64–22.7, p = 0.0088), culture-proven sepsis (odds ratio 17; 95% CI: 0.92–322, p = 0.072), and normal vaginal delivery (odds ratio 6.5; 95% CI: 1.7–25.4, p = 0.032) were found as statistically significant risk factors for development of ABE. **Conclusion:** Nearly half of the neonates admitted in a tertiary care NICU with severe hyperbilirubinemia had features of ABE on admission. The risk was more if they were born vaginally, had a lower weight on admission, had blood group incompatibility with positive Coomb's test, and had sepsis.

Keywords: Hyperbilirubinemia, Blood Groups, ABE.

Introduction

Some degree of neonatal jaundice or hyperbilirubinemia is an unpreventable condition in 60%-80% of newborns worldwide[1,2]. In a proportion of infants, jaundice may become severe, progressing to acute bilirubin encephalopathy (ABE) or kernicterus with a significant risk of neonatal mortality[3,4]. Surviving infants

may acquire long-term neurodevelopmental sequelae such as cerebral palsy, sensorineural hearing loss, intellectual difficulties or gross developmental delays[5,6]. Available clinical guidelines recommend early detection of infants at risk of severe hyperbilirubinemia to facilitate timely and effective prevention of the associated burden[7,8]. Current evidence however, suggests that low- and middle-income countries (LMICs) disproportionately bear the burden of severe neonatal hyperbilirubinemia[9,10]. For example, in one recent review on the global burden of hyperbilirubinemia, sub-Saharan Africa and South Asia were reported as the leading contributors to an estimated 1.1 million babies who would develop severe hyperbilirubinemia worldwide every year[9]. Another systematic review found that LMICs consistently report substantially higher rates of exchange transfusion and bilirubin-induced neurologic dysfunctions (acute bilirubin encephalopathy (ABE) and chronic bilirubin encephalopathy or kernicterus) than in high-income countries[10]. The challenge of managing infants with ABE and kernicterus and their sequelae is daunting especially in resource-constrained settings[11-14]. Early identification of infants at risk of severe hyperbilirubinemia is therefore, even more crucial to curtailing the burden of this ubiquitous and potentially devastating condition within the first 14 days of life[15]. However, the underlying risk factors in LMICs have not been systematically explored to guide necessary clinical and public health interventions.

Material and methods

This prospective study was conducted Department of Pediatrics, Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar, India for 1 year

Methodology

All consecutive neonates more than 35 weeks of gestation admitted in the NICU with a serum bilirubin >20 mg % in first 72 h of life or >25 mg% after first 72 h formed the study subjects[16]. Neonates with Apgar score <3 at 5 min, hypoxic ischemic encephalopathy at stage 3, major congenital malformations, conjugated bilirubin >2 mg%, metabolic disorders, and meningitis were excluded. Baseline characteristics of the neonates and their mothers were noted. The neonates were followed closely during the hospital stay. ABE was diagnosed in the presence of the following clinical features: Early phase (Stage I): hypotonia, lethargy, high pitched cry, and poor suck; Intermediate phase (Stage II): irritability, opisthotonos, seizures, apnea, oculogyric crisis, hypertonia, and fever; and Advanced phase (Stage III): pronounced opisthotonos, shrill cry, apnea, seizures, and death[17]. The neonates were managed according to the American Academy of Pediatrics, 2004 guidelines[18]. Phototherapy units used were Compact Fluorescent Lamp (CFL), fiberoptic, and light emitting diode (LED) with the spectral irradiance of 10–30 mW/cm2/nm. Double volume exchange transfusion (ET) was performed as an is volumetric procedure by the umbilical vein or by peripheral artery and vein using fresh whole blood. For Rh is immunization, Rh negative and blood group 'O' or that of the baby's suspended in AB plasma, cross-matched with baby's and mother's blood was used; for ABO incompatibility, Rh compatible and blood group 'O' (not that of the baby) suspended in AB plasma, cross-matched with baby's and mother's blood was used; and for other situations, baby's group and Rh type, cross-matched with baby's and mother's blood was used for ET.

All neonates were investigated for serum bilirubin (direct, indirect, and total by photometric test using 2,4-dichloroaniline), blood group, hematocrit, reticulocyte count, Coomb's test, G6PD levels, serum albumin, and blood culture. All neonates were followed up closely during hospitalization. Enrolment was done in the initial 6-month period. Discharged neonates were followed in OPD at 1, 3, and 6 months

of age. Neurological assessment of the neonates was done in accordance with the age specific norms, as per Amiel-Tison.[19] Audiological evaluation was done at 3 months of age by Oto Acoustic Emission (OAE) and Brain stem evoked reflex audiometry (BERA) at 3 months of age. Infant showing any of the following features on follow-up were designated to have Chronic Bilirubin Encephalopathy (CBE): tone abnormality, upward gaze palsy, abnormal OAE/Brain stem evoked audiometry (BERA), and choreoathetoid movements[17].

Statistical methods

Data were analyzed using statistical software package, STATA 8.2. Proportions were compared using chi-square statistics and the risk was presented in terms of odds ratio (OR) with 95% confidence interval (95% CI). Fisher's exact p-value was reported. Two sample t tests were used to see the difference between the means of two different groups, if data were normally distributed. If data were not normally distributed, a non-parametric equivalent of two-sample t-test was used. Mann–Whitney test was used to test the level of significance.

Results

A total of 80 neonates were enrolled. All patients were out born. Causes of jaundice in the study neonates were Rh incompatibility in 21 (26.25%), ABO incompatibility in 32 (40%), cephalhematoma in 3 (3.75%), breast milk jaundice in 3 (3.75%), and unknown etiology in 21 (26.25%). Among 80 neonates enrolled, 30 (37.5%) had ABE (Stage 2, 3) on admission. 5 with ABE left against medical advice within 48 h of admission. Of the 75 neonates that left, 6 (8%) died and 69 (92%) were discharged. 3 patients died due to ABE in the ABE group and 3 due to sepsis in the group without ABE. Out of 50 neonates who did not have ABE on admission, none developed it during hospital stay. As shown in Table 1, both the study groups were comparable with respect to age (125.21±77.85h vs135.54±75.19 h; p = 0.63), sex (male/female 2.1:1 vs 1.39:1; p = 0.74), presence of SGA babies (4[13.33%] vs 4 [8%]; p = 1.22), socioeconomic status (p = 0.48), and antenatal care (p = 1.2). However, neonates with ABE weighed less on admission than those without ABE (2324.87±429.69 g vs 2531.87±382.91 g; p = 0.027) and the causes of hyperbilirubinemia (p = 0.033).

Of 30 neonates with ABE, 19 presented in stage II and 11 presented in stages III of ABE. Table 2 shows the risk factors associated with development of ABE. A lower weight on admission (2331.886±397 g vs 2511.87±379 g; p = 0.023), ABO/Rh incompatibility (odds ratio 4.20; 95% CI: 1.23–14, p = 0.037), a positive Coomb's test (odds ratio 6.1; 95% CI: 1.64–22.7, p = 0.0088), culture-proven sepsis (odds ratio 17; 95% CI: 0.92–322, p = 0.072), and normal vaginal delivery (odds ratio 6.5; 95% CI:1.7–25.4, p = 0.032) were found as statistically

significant risk factors for development of ABE. However top feeding (odds ratio = 0.68; 95% CI: 1 8–2.8, p = 5.63), early discharge from the hospital (odds ratio 1.41; 95% CI: 0.31–5.6, p = 0.69), history of jaundice in another sibling (odds ratio =1.5; 95% CI: 0.46–3, p = 0.72), G-6-PD deficiency, and hypoalbuminemia (serum albumin <2.5 g/dl) were not significant as risk factors for ABE. The odd of association of delivery conducted at home with ABE was 6, but it was statistically not significant (odds ratio 5.5; 95% CI: 0.42–52.3, p = 0.14).

28 neonates of the group with ABE and 42 of the group without ABE were discharged. In ABE group, 28 (93.33%) turned up for follow-up and 45 (90%) had evidence of CBE. In no ABE group, only 35 (70%) neonates came for follow- up. All of them had normal neurological examination on follow-up except one who had increased tone at 1-month follow-up but did not return for further follow-ups. Of 80 neonates

studied, OAE as a screening was done in all and was found to be normal in all. BERA could be done in only 10 neonates, and it was normal in all of them. MRI could not be done in any of them due to financial constraints.

Discussion

The primary objective of our study was to determine the outcome of neonates with severe hyperbilirubinemia. The high prevalence could be because of lack of pre-discharge assignment of hyperbilirubinemia in most health facilities in our area, lack of awareness about the proper management of neonatal jaundice, and paucity of well-functioning intensive phototherapy units. Overall mortality was 7.5% and ABE related mortality was 2.5%. Of the 80 neonates enrolled in the present study, 30 (37.5%) had ABE on admission. The occurrence of a poor outcome was much less in other studies from the west. Johnson et al. from pilot USA kernicterus registry reported clinical signs of ABE in 7 of 125 (5.6%) infants[20]. Manning et al. observed that 14 out of 108 (12.9%) infants with hyperbilirubinemia had evidence of bilirubin encephalopathy and out of these 3 (2.7%) died[21]. Newman et al. reported that out of 140 newborns with bilirubin level >25 mg/dl, none had kernicterus, but 14 had questionable or abnormal neurological examination[22]. This may be because neonates of Asian origin are more susceptible for developing ABE[23]. A study from India by Murki et al. reported ABE in 21.8% of 64 neonates with serum bilirubin >18 mg%[23]. The lower incidence of ABE in this study as compared to ours was because they only included neonates without hemolysis.

One of the risk factors found by us to be associated with ABE was lower weight on admission. In our study the actual birth weight and the gestation of most of the neonates were not known as all the cases were out born. It is possible that a lower weight on admission in ABE patients was due to their being <35 weeks gestation or due to the presence of some dehydration. Both the factors are implicated in causing BIND. In our study, 90% of neonates with ABE were delivered vaginally in comparison to 68% in those without ABE. This observation is similar to that reported by Murki et al. where 90% of kernicteric babies had been delivered vaginally as against 74% neonates without kernicterus[23]. The reason could be that babies born vaginally are discharged early from the hospital.

We found that more neonates who were discharged early developed ABE than those discharged after 48 h. However, this was statistically not significant. Early discharge of neonates from the hospital causes delayed diagnosis of jaundice and an increased risk of kernicterus as reported by Harris et al. who in their study of 6 term neonates with serum bilirubin levels >25 mg % reported ABE in 80% of cases discharged within 48 h of birth[24]. Similarly, a Canadian study concluded that high readmission rate within days after initial discharge indicates a need for a more thorough assessment of newborn infants and consideration of strategies to identify at-risk newborns, such as pre discharge measurement of serum bilirubin[25].

Infections predispose a neonate for ABE by increasing the permeability of the blood brain barrier to bilirubin. Also, the binding of bilirubin to albumin, uptake of bilirubin into hepatocytes for conjugation, and the process of conjugation are all known to be stunted in the presence of sepsis[10]. We found that culture-proven septicaemia was significantly associated with development of ABE. The same association is reported by Hanko et al.[18]. However, in a study which included only 6 neonates, this association was not found[16].

Of the 30 neonates with ABE, 13 (43.33) were Coomb's test positive. However, in the group without ABE, only 6 (12) were Coomb's test positive. The difference was statistically significant ($p = 0.0088$). E. Hanko and R. Lindemann in their study of

3 neonates with kernicterus reported ABE developing in none of the neonates having positive Coomb's test[26]. This was also observed by F. Ebbesen and a Canadian study[25].

Unlike the findings of Murki et al. who reported that the proportion of neonates receiving exclusive breast feeding was lesser (57%) in babies with kernicterus compared to those without kernicterus (80%)[23], we found that feeding practices of the neonates were not risk factors for development of ABE.

Various hypotheses have been proposed for the increased propensity of Asian and Africans to bilirubin toxicity. Increased prevalence of G6PD deficiency is one major factor as reported by Stevenson et al.[27] A surveillance study in UK and Ireland demonstrated that ethnic group (black) and glucose 6-phosphate dehydrogenase deficiency independently increased the risk of encephalopathy in infants with hyperbilirubinemia.[21] In our study, G6PD deficiency was not found in any of the neonates studied.

In our study, the mean age at admission of neonates with ABE and without ABE was similar between 5 and 6 days. There was a male preponderance in both the groups and the difference was not statistically significant. Similarly, in the study by Murki et al., the mean age on admission of neonates with ABE was 5.5 days with a male predominance, 2.5:1 in kernicteric, and 1.17:1 in non-kernicteric babies[23]. Also, in their study, the number of SGA babies was more in the kernicteric group (21.4%) than non-kernicteric group (6%). In our study, however, both the groups had 3 SGA neonates.

The levels of free bilirubin are higher in jaundiced neonates with lower serum albumin and hence the chance of developing ABE is greater. However, we found serum albumin levels to be similar in both kernicteric and non-kernicteric babies. This was also found by Murki et al.[23]

In the 6-month follow-up, we found that 90% of neonates admitted with ABE developed CBE despite being treated with standard guidelines. Only 2 neonates who did not have ABE on admission had increased tone at 6 months of age. So, the newborns admitted without ABE and managed by standard guidelines had normal outcome in all of the cases except one. Similar study by Kanya Mukhopadhyay showed that at 1 year, 80% had abnormal neurodevelopment[28].

In our study, we found that the actual level of serum bilirubin does not affect development of ABE rather it is the presence or absence of the risk factors which makes the difference. The study done by Gamaledin et al. also concluded that the great variation in response to total serum bilirubin (TSB) indicates that the biological factors other than TSB value are important in the pathogenesis of ABE[29].

There are several limitations of the present study. One was that we did not estimate free bilirubin levels, pH and hydration status of our subjects and we could not do MRI for any of our subjects due to financial reasons. Also, we could not do BERA in all the cases. Because of finite study duration, we could follow our infants only for a period of 6 months. Some infants could have shown improvement or deterioration in neurological examination if followed up further.

The strength of the study is that the dropout rate was small and 81.8% of neonates were followed up for 6 months.

It is evident from the study that the neonates with intermediate and advanced phase of ABE had poor outcome despite adequate management. It was reassuring that 97% of the neonates with severe hyperbilirubinemia but no ABE on admission responded well when managed according to the AAP 2004 guidelines. Most of our study population was out born. The lack of concern of healthcare personnel regarding occurrence of severe hyperbilirubinemia is reflected in our study.

There is a lack of protocol to measure pre discharge bilirubin in neonates being discharged early and a paucity of effective intensive phototherapy units in birthing hospitals in our region. These could be the reasons for a dismal outcome of neonates with severe hyperbilirubinemia in our study.

Conclusion

Nearly half of the neonates admitted in a tertiary care NICU with severe hyperbilirubinemia had features of ABE on admission. The risk was more if they were born vaginally, had a lower weight on admission, had blood group incompatibility with positive Coomb's test, and had sepsis.

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