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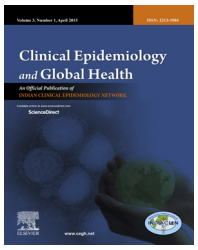

Original Article

Outcome of neonates with severe hyperbilirubinemia in a tertiary level neonatal unit of North India

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ABSTRACT

Objectives: The primary objective was to determine the outcome, in terms of mortality and development of bilirubin encephalopathy, of neonates with severe hyperbilirubinemia. The secondary objective was to determine the possible risk factors for development of acute bilirubin encephalopathy (ABE).

Methods: Consecutive neonates of >35 weeks gestation admitted to Neonatal Intensive Care Unit (NICU) with a serum bilirubin >20 mg% in first 72 h of life or >25 mg% later were enrolled in the study. The clinical and demographic characteristics of the neonates were recorded. Neonates were treated with phototherapy and exchange transfusion as required.

Outcome in terms of mortality and development of bilirubin encephalopathy was noted. Discharged neonates were followed at 1, 3, and 6 months for chronic bilirubin encephalopathy (CBE).

Results: Out of 64 neonates enrolled, 28 (44%) were admitted with ABE. Four with ABE left against medical advice. Out of 60 neonates studied, 5 (8.3%) expired. A total of 17 (89.5%) neonates of ABE group and 25% of all neonates developed CBE on follow-up. A lower weight on admission (2254.68 + 417 g vs 2481.75 + 369 g; $p = 0.0195$), ABO/Rh incompatibility (odds ratio 4.00; 95% CI: 1.13–14, $p = 0.030$), a positive Coomb's test (odds ratio 5.7; 95% CI: 1.53–21.4, $p = 0.0096$), culture-proven sepsis (odds ratio 16; 95% CI: 0.82–312, $p = 0.067$), and normal vaginal delivery (odds ratio 5.5; 95% CI: 1.1–27.4, $p = 0.037$) were found to be 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.

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1. Introduction

Neonatal jaundice is feared due to its potential to cause Bilirubin Induced Neurological Dysfunction (BIND). After the universal use of rhesus immunoglobulin in developed countries, the incidence of kernicterus decreased remarkably, so much so that it became a rare identity and gradually pediatricians became complacent about hyperbilirubinemia. American Academy of Pediatrics had recommended 25–29 mg/dl of serum bilirubin as the cut-off for exchange transfusion in term babies with non-hemolytic jaundice based on the extremely rare occurrence of kernicterus in this group.[1,2] However there was a resurgence of kernicterus in the 1990s due to non-hemolytic causes. This happened in temporal association with profound changes in maternal (enhanced prevalence of breastfeeding) and medical (early hospital discharge) behaviors.[3] A pilot kernicterus registry in the United States shows 125 babies with kernicterus enrolled in the registry from 1984 to 2002. All but 4 (97%) of these babies had been discharged from hospital in less than 72 h after birth.[4] Another pilot USA registry concluded that the increase in the kernicterus cases was due to inability to identify at-risk infants and to manage them in a timely manner.[5] In Denmark, 8 cases of kernicterus were reported from 1994 to 2002, whereas no cases had been reported for the preceding 20 years.[6] Between, 2002 and 2005, a more vigilant approach was taken for the management of newborn jaundice, and no more cases were reported.[7] A study from India done by Murki reported an incidence of 21.8% of kernicterus in neonates with non-hemolytic hyperbilirubinemia.[8] Kanya Mukhopadhyay from India studied newborns with ABE and followed them up for their neurodevelopmental outcome. She did not study the risk factors associated with ABE.[9]

These observations prompted us to find the overall occurrence and the risk factors for development of ABE and CBE in our part of the country where bilirubin levels greater than 30 mg/dl, presence of ABE at the time of admission, and inadequate treatment are rampant.

2. Methods

This prospective observational study was conducted over a period of 1 year in a level III NICU and outpatient department of Pediatrics of a tertiary care teaching hospital after seeking approval from the institute's ethics committee. An informed consent was obtained from the parents before enrolment of the neonates. 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.[10] 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.[11] The neonates were managed according to the American Academy of Pediatrics, 2004 guidelines.[12] Phototherapy units used were Compact Fluorescent Lamp (CFL), fiberoptic, and light emitting diode (LED) with the spectral irradiance of 10–30 $\mu W/cm^2/nm$. Double volume exchange transfusion (ET) was performed as an isovolumetric procedure by the umbilical vein or by peripheral artery and vein using fresh whole blood. For Rh isoimmunization, 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.[13] 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.[11]

2.1. *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 between two values. Difference between two values was considered to be significant if p value was found to be <0.05.

3. Results

During the study period, a total of 128 neonates met the inclusion criteria. Of these, 64 neonates were not included as 28 were preterm, 10 had meningitis, 22 had HIE and 4 had major congenital malformations. A total of 64 neonates were enrolled. All patients were outborn. Causes of jaundice in the study neonates were Rh incompatibility in 15 (25%), ABO incompatibility in 25 (41.6%), cephalhematoma in 2 (3.3%), breast milk jaundice in 2 (3.3%), and unknown etiology in 16