Evaluation of Risk Factors for Exchange Range Hyperbilirubinemia and Neurotoxicity in Neonates from Hilly Terrain of India

Abstract

Background and Aim: Neonatal hyperbilirubinemia continues to be the most common cause of hospital admissions and readmissions in the neonatal population worldwide and this pattern continues despite attempts to identify neonates at risk of pathological hyperbilirubinemia. Therefore, this study aimed to study the risk factors for severe hyperbilirubinemia in neonates.

Materials and Methods: An observational prospective study was undertaken for 1 year in neonates with hyperbilirubinemia requiring double volume exchange transfusion in neonatology unit of a tertiary rural health care hospital. Results: Risk factors included ABO incompatibility in 14 (28.5%), Rh incompatibility in 14 (28%). Other risk factors for hyperbilirubinemia were, jaundice in elder sibling, oxytocin use, birth asphyxia, hypothyroidism, ABO along with Rh incompatibility, Glucose-6 phosphate Dehydrogenase deficiency, cephalhematoma, and sepsis in neonates. Ten (20%) neonates were neurologically abnormal with signs of encephalopathy. Significant association of risk factors with neurotoxicity were also found. All neurologically abnormal neonates were small for date and none was appropriate for date \((P = 0.05)\). There were no neurologically abnormal neonates with A+ and O− mothers \((P = 0.04)\). Conclusion: The high rate of exchange transfusion warrants aggressive management of neonatal hyperbilirubinemia by health-care providers by adequate dissemination of information, strict following of hour-based normograms, performing total serum bilirubin assessment in all icteric neonates, and stratification into risk groups thereafter.

Keywords: Kernicterus, neonatal hyperbilirubinemia, risk factors

Introduction

In neonates with severe hyperbilirubinemia, indications for exchange transfusion include exchange range hyperbilirubinemia, phototherapy failures, and features of acute bilirubin encephalopathy (ABE) in neonates. However, despite increasing knowledge about risk factors, the prevalence continues to be more in developing nations. As a result, a sentinel event alert was issued by the US centers for disease control and prevention to identify cases of kernicterus in healthy term infants. The study attempts to study the risk factors for severe hyperbilirubinemia due to its mortality and long-term neurological sequelae.

Materials and Methods

This was a hospital-based prospective observational study, conducted in the neonatology unit, of a tertiary care hospital (2013–2014).

The study commenced after approval from protocol and ethical committee.

Written informed consent was obtained from all the parents/guardians of the enrolled subjects. All neonates presenting with neonatal hyperbilirubinemia with gestation ≥35 weeks with hyperbilirubinemia in exchange range according to the AAP (American Academy of Pediatrics) guidelines were included in the present study. Exclusion criteria were neonates with gestation <35 weeks, neonates with conjugated hyperbilirubinemia and persistence of hyperbilirubinemia beyond 4 weeks of life. Detailed history, examination, and investigations were performed, followed by classification of neonates into zones according to total serum bilirubin levels as per the AAP guidelines. The total serum bilirubin levels were measured using Pearlman and Lee Diaz method.

Investigations conducted in all neonates requiring exchange were total serum bilirubin (TSB), conjugated and unconjugated fractions of TSB, ABO and Rhesus blood group, direct coombs
test (DCT), reticulocyte count and peripheral blood smear examination. Glucose-6-phosphate dehydrogenase (G6PD) levels, thyroid profile, and sepsis screen were done wherever indicated.

**Statistical analysis**

Microsoft office (excel) 2010 Home edition was used for statistical analysis. Chi-square test was used for categorical variables. The value of $P < 0.5$ was considered statistically significant.

**Results**

Out of the total 1970 neonates admitted to the neonatal unit, 432 (21.9%) had neonatal jaundice requiring phototherapy. While 60 (13.8%) neonates required exchange transfusion and 49 (11.3%) neonates who fulfilled the inclusion criteria were studied. Of these, 22 (45%) were females and 27 (55%) were males. Male-to-female ratio was 1.2:1. Majority of total infants i.e., 37 (76%) were SFD, whereas 12 (24%) were appropriate for date (AFD) [Table 1].

The family history of jaundice in elder sibling was present in 7 (14%) cases, whereas oxytocin use in 7 (14%) neonates. There was no history of delayed cord clamping in any patient. History of oxytocin use was present in 7 (14%) neonates. History of birth asphyxia was present in 2 (4%). In both cases, it was mild. History of delayed feeding or meconium passage was not present in any of the neonates. On examination, cephalhematoma was present in 2 (04%) neonates.

Out of the total 49 neonates, ABO incompatibility was present in 14 (28.5%) neonates and Rh incompatibility in 14 (28%) neonates. ABO along with Rh incompatibility was present in 4 (8%) neonates. DCT was positive in 12 (85.7%) neonates with ABO incompatibility and 13 (92.8%) neonates in Rh incompatibility. G6PD deficiency was present in 2 (4%) neonates. History of hypothyroidism was present in 5 (10%) mothers, and these mothers were receiving treatment for the same. Three (06%) neonates had abnormal thyroid profile on investigations [Table 2].

Among the total 49 mothers distribution of various blood groups were A Rh−06 (12.2%), A Rh+ 02 (4.1%), AB Rh−01 (2.0%), AB Rh+ 03 (6.1%), B Rh−04 (8.2%), B Rh+ 16 (32.7%), O Rh−04 (8.2%), and O Rh+ 13 (26.5%). Among the total 49 neonates blood groups were A Rh−01 (2.0%), A Rh+ 15 (30.5%), AB Rh−0 (0%), AB Rh+ 03 (6.1%), B Rh−0 (0%), B Rh+ 22 (44.9%), O Rh−0 (0%), and O Rh+ 08 (16.3%).

More than one double volume exchange transfusion (DVET) was required in 4 (8%) patients. Of these, 3 (75%) neonates required exchange transfusion twice and 1 (25%) neonates required exchange transfusion thrice. Of the 4 neonates who required more than one exchange transfusion, Rh incompatibility was present in 1 neonate; ABO along with Rh incompatibility was present in 1 neonate while no cause could be ascertained in 2 neonates. The mortality among the studied neonates was 2 (4%) of the total. Both of these were female neonates with features of ABE. There were total 10 neurologically abnormal neonates among 49 [Table 3].

**Discussion**

This prospective study focused on studying the risk factors for exchange range hyperbilirubinemia. Till date, only two Indian studies have outlined these risk factors and none so in the last decade. The risk factors were studied for a high rate of exchange transfusion in this hilly part of India.

The mean period of gestation of neonates in our study was 38.3 ± 1 weeks which was identical to available studies. While mean age of presentation in our study was 98 ± 49 h, available literature has reported the age of presentation in days as 4 ± 1 days, 4.9 ± 2.2 days, and 111.6 ± 66 days.

This wide range in age of presentation can be explained due to differences in the basic etiology underlying hyperbilirubinemia such as ABO incompatibility, G6PD deficiency, and extravasation in the form of cephalhematoma. Mean age at which icterus was first noticed either by relative or health-care provider was 51 ± 39 h. However, the mean age of presentation was 98 ± 49 h showing a lag period between first notice of icterus and presentation. This could be due to multifactorial causation like delay in seeking care, delayed referral, phototherapy failure, and sociocultural factors.
The percentage of male neonates among those requiring exchange were 55% and female neonates were 44% with male-to-female ratio of 1.2:1. This was almost identical to the available literature. All studies showed male preponderance among neonates with severe hyperbilirubinemia. Hence, male sex has emerged as a well-recognized risk factor for exchange range hyperbilirubinemia in neonates. The mean of preexchange TSB level was 27.1 ± 10 mg/dl. This was reported to be 30 mg/dl by Bhat et al., Davutoğlu et al., and Badiee et al. All these studies showed bilirubin levels >25 mg/dl to be uniformly present in neonates requiring exchange transfusion. In the current study majority of total infants, that is, 76% were SFD and rest, 24% were AFD. The study demonstrates a preponderance of small for date neonates to develop severe hyperbilirubinemia requiring exchange transfusion with statistically significant results.

ABO incompatibility was the most common reason for exchange range hyperbilirubinemia in all available studies. It was defined as DCT positivity and or evidence of hemolysis in the peripheral blood film. In the present study, it was present in 32% infants (62% male and 38% of female neonates). Variable incidence of 35.9%, 5%, 25%, 38%, 32%, 22%, and 15% has been reported in available literature.

Rh incompatibility defined as DCT positivity and or evidence of hemolysis in peripheral blood film was present in 28% of patients. Studies by Bhat et al., Davutoğlu et al., Badiee et al., Dikshit et al., and Chitlangia et al. had reported Rh incompatibility in 20.6%, 12.6%, 11.7%, 10.7%, 9.2%, and 6.7%, respectively.

Rh incompatibility was the second most common reason for exchange transfusion in neonates. Among all the studies our study reflected the highest rate of Rh incompatibility in neonates reflecting geographical and racial variations. G6PD deficiency was detected in 4% of the total subjects while previous studies show rates of 19.1%, 17.2%, 11.4%, 20.6%, 12.6%, 11.7%, 10.7%, 9.2%, and 6.7%, respectively.

The percentages of neonates with G6PD deficiency remain low in our study. This can be explained by low detection rate during the acute hemolytic episode as young red blood cells have higher G6PD activity. More accurate assessment can be done if these neonates are followed up for G6PD deficiency testing subsequently.

Sepsis was present in 8.1% of the total patients in our study. Only two other studies by Narang et al. and Dikshit et al. have reported the incidence of sepsis in neonates requiring exchange transfusion. It was reported to be 24% and 8%, respectively. However, the higher rate reported by Dikshit et al. may be due to more number of sick infants referred to their hospital. Extravasation in the form of Cephalhematoma in the current study was

The mean body weight in our study was 2.58 ± 0.38 kg, Previous studies show mean body weight to be 2.81 ± 0.67 with minimum of 1.2 kg and maximum of 4.3, 2.53 ± 0.52, and 3.36 ± 0.48 kg.
present in 4% of all the neonates. Narang et al.\textsuperscript{[6]} reported that 1.4% of neonates had extravasation. However, no other recent studies have described the association between the exchange range hyperbilirubinemia and extravasation among their patients. History of jaundice in eldersibling was present in 14% of cases in our study which has not been described in any previous study. This is a pointer towards the role of genetic factors in the causation of severe hyperbilirubinemia requiring exchange transfusion. Documented hypothyroidism was present in 6% of the neonates in our study. Only Sgro et al.\textsuperscript{[10]} have reported hypothyroidism in neonates with severe hyperbilirubinemia in 1% of neonates in whom the causes could be found. No cause for exchange range hyperbilirubinemia could be ascertained in 16% of the total study patients in our study. Previous studies have reported rates of 9.3% by Dikshit et al.,\textsuperscript{[5]} 13.9% by Davutoğlu et al.,\textsuperscript{[8]} 27.5% by Chitlangia et al.,\textsuperscript{[9]} 35.4% by Narang et al.\textsuperscript{[6]} The wide variation in the percentage of idiopathic cases can be due to genetic mutations in enzymes involved in bilirubin production and metabolism in addition to the regional differences and resource availability among various studies.

The mortality rate among the study subjects was 2 (4%) and these were two female neonates who presented with features of ABE i.e. abnormal tone, retrocollis, seizures, poor feeding and lethargy and died within 24 h of presentation. This mortality was chiefly attributed to ABE as suggested by signs and symptoms. The mortality rate in other studies has been documented to be 1.5% by Badiee,\textsuperscript{[12]} 2% by Bhat et al.,\textsuperscript{[7]} 1.5% by Chitlangia et al.,\textsuperscript{[9]} zero by Davutoğlu et al.,\textsuperscript{[8]} zero by Narang et al.\textsuperscript{[6]} All these studies show that exchange transfusion is a relatively safe procedure, especially in experienced hands. However, with decreasing rates of exchange, increasing rate of complications is expected, more so in developed nations where the residencies may be completed without seeing or performing even a single exchange transfusion.

More than one DVET was required in 8% of patients in our study. In one of these RH incompatibility was present, in another both ABO plus RH incompatibility were present while in two no cause could be ascertained. Total 6% of neonates required DVET twice and 2% of neonates required DVET thrice. The percentage of neonates requiring more than DVET are 12.6% by Davutoğlu et al.,\textsuperscript{[8]} 12.3% Badiee et al.,\textsuperscript{[12]} and 11.7% by Chitlangia et al.,\textsuperscript{[9]} Chitlangia et al.\textsuperscript{[9]} have also described their findings that DVET was done twice in 9.2%, thrice in 1.7%, 5 times in 0.8% of the total neonates. These findings show declining trend for multiple DVET which can be best explained by more intensive phototherapy and availability of alternate modalities like immunoglobulins.

In the present study, total of 49 subjects, 20% of neonates were neurologically abnormal with signs of encephalopathy. Other studies have reported the percentage of neurologically abnormal neonates as 7.3%, 16.5%, and 19.8%.\textsuperscript{[8,10,12]} In the current study, 90% of neonates were between 35 and 37 weeks, whereas 10% of neonates were between 37 and 41 weeks (P = 0.289) reflecting differences between preterms and term neonates and higher predisposition for neurological damage in preterms. Previous studies have reported the number of preterms with respect to the total study subjects as 6.3% by Davutoğlu et al.\textsuperscript{[8]} who has also described prematurity and other factors. His study also reported prematurity and kernicterus 40%, prematurity and ABO incompatibility 5.1%, prematurity and Rh incompatibility 1.3%, prematurity and polycythemia 1.3%, prematurity and hypothyroidism 1.3% of the total neonates. Crosse et al.\textsuperscript{[14]} reported that 73.6% of preterm babies with kernicterus died as compared to 25.6% of all preterm infants. However, limited studies have compared prematurity versus risk for neurological abnormality in neonates.

Of the total 10 neurologically abnormal neonates all 100% were SFD and none was AFD (P = 0.50) showing differences between the two however not significant statistically. However To the best of our knowledge, detailed comparison of growth retardation versus neurological Abnormality in neonates with severe hyperbilirubinemia was not found in the previous studies.

This calls for better screening and more intensive management of growth retarded neonates. The distribution of blood groups among the total 49 neonates was A Rh−01 (2.0%), A Rh+ 15 (30.5%), AB Rh−0 (0%), AB Rh+ 03 (6.1%), B Rh−0 (0%), B Rh+ 22 (44.9%), O Rh−0 (0%), and O Rh+ 08 (16.3%). Among 10 neurologically abnormal neonates, 5 (50%) had blood Group A Rh+, 3 (30%) had blood Group B Rh+, 1 (10%) each had blood Group AB Rh+ and A Rh+ and none of the neonates were O Rh+, O Rh−, AB Rh− and B Rh− (P = 0.77) showing no significant differences in rates of neurological abnormality with different blood groups. The relation of blood groups to neurological status has not been described in detail in neonates with hyperbilirubinemia requiring exchange transfusion in the available literature.

Among the total 10 neonates with abnormal neurological examination, 3 (30%) neonates had mothers with A Rh−blood Group, 2 (20%) had mothers with AB Rh+ blood Group, 2 (20%) had mothers with B Rh+ blood group and 1 (10%) each had mother with blood Groups AB Rh−, B Rh−and O Rh+. While there were no neurologically abnormal neonates with A Rh+ and O Rh−mothers (P = 0.042) showing statistically significant differences in rates of neurological abnormality. So far no studies have discussed the detailed analysis of maternal blood group with the abnormal neurological status of the neonate. However, the current study has reflected

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Conclusion

Identification of risk factors predisposing to exchange range hyperbilirubinemia and neurotoxicity prediction in healthy near term and term neonates can help in the stratification of high-risk group. Management of neonatal hyperbilirubinemia with strict following of hour based normograms can further result in decrease into morbidity, mortality, and neurotoxicity resulting into neurodevelopmental disorders.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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