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Original Research Article

A Prospective Cohort Study to Evaluate the Early Indicator of Significant Hyperbilirubinemia in Healthy Full-term Infants at 72 hrs of Age

Amit Kumar[1], Mani Shankar[2]

[1]Assistant Professor, Department of Pediatrics, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India

[2]Assistant Professor, Department of Pediatrics, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India

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Corresponding author: Dr. Mani Shankar
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Abstract

Aim: This study aims to evaluate the early indicator of significant hyperbilirubinemia in healthy full-term infants at 72 hrs of age.

Methods: This prospective observational study was conducted in the Department of Pediatrics, Darbhanga medical college, and Hospital, Laheriasarai, Darbhanga, Bihar, India, for 12 months. Full-term newborn delivered at our hospital of >36 weeks of gestation. Birth weight >2 kg was included in this study. Bilirubin level at or above high intermediate risk zone at 24 and 48 hrs of age was considered a cut-off value to find out the association with significant hyperbilirubinemia at 72 hrs of age.

Results: Of 100, 54% of the newborn were male, and 46% were female. 91(91%) newborns included were between 37 to 40 weeks, and 9% were above 40 weeks of gestation. 85(85%) were appropriate for gestational age, 12 newborns (12%) were short, and three newborns were large. Five newborns (33.33%) developed hyperbilirubinemia; nine (30%) newborns developed subsequently developed hyperbilirubinemia at 72 hrs.

In study groups, the median values for gestational age and birth weight were 38 weeks, 3.1 kg, respectively. Twelve newborns (12%) showed signs of dehydration, and out of these 12 newborns, 7 developed hyperbilirubinemia subsequently at 72 hrs of life. In addition, 31% received top feeding or mixed feedings, while 17% of newborns' first feeding was delayed for more than 3 hrs due to inadequate lactation on the first few days. In our study, birth weight <2.5 kg, delayed first feeding, dehydration, and 48 Hr serum bilirubin >11.8 mg/dl were associated with significant hyperbilirubinemia($p<0.05$).

Conclusion: The present study concluded that healthy full-term newborns with birth weight <2.5 kg, higher 24 and 48-hour serum bilirubin were more likely to experience significant hyperbilirubinemia who are often discharged from hospital early.

Keywords: Total serum bilirubin, Neonatal Hyperbilirubinemia, Risk factors, Significant hyperbilirubinemia, Full-term newborn

Introduction

Sixty to 80% of healthy, full-term infants are expected to present with idiopathic neonatal jaundice in the initial postnatal period.1 Idiopathic neonatal jaundice is attributed to an increased breakdown of heme, immature liver function, low amount of intestinal bacteria, increased enter the hepatic circulation of bilirubin, and inadequate intake.2 Indicators of inadequate intake include 4 to 6 thoroughly wet diapers in 24 hours and the passage of 3 to 4 stools per day by the fourth day. In addition, the stools of adequately breastfed infants should change from meconium to a mustard yellow, mushy stool by the third to fourth day. These assessments help identify breastfed infants at risk of dehydration because of inadequate intake. However, it is relatively subjective due to individual differences.3

Compared to other methods, body weight loss (BWL) percentage is an objective and valuable tool that may indicate when interventions such as supplemental feeding should be considered.

Previous studies have suggested that 7% to 10% BWL by day 3 in fully breastfed infants is abnormal neonatal BWL.4,5 However, there are conflicting opinions about what constitutes average neonatal BWL and when supplemental feeding should be considered to prevent significant hyperbilirubinemia. This study aimed to analyze the optimal cutoff values of BWL percentages in the first three days after birth to predict neonatal hyperbilirubinemia 72 hours after birth.

Material and methods

This prospective observational study was conducted in the Department of Pediatrics, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India, India, for 12 months

Inclusion criteria

- Full-term newborns delivered at our hospital of >36 weeks of gestation
- Birth weight >2 kg

Exclusion criteria

- Newborns requiring admission to NICU
- Infants of a diabetic mother
- Newborns with major congenital malformations
- Birth trauma, newborns with hemolytic anemias (Rh, ABO incompatibility)
- Neonatal sepsis

Methodology:

One hundred patients were included in this study. The study was conducted after taking ethics committee approval and prior informed consent from parents. Demographic profile and relevant information was collected by using structured Pro- forma by interviewing the mother and from the mother's case sheet. Gestational age was assessed by New Ballard score. Venous blood samples were collected from the baby at 24, 48 hours, and 72 hrs of life. The venous blood sample was collected, and serum bilirubin estimation was done within 12 hours of collecting the sample by Diazotized sulfanilic test.

According to the Bhutani nomogram, bilirubin levels were analyzed to find the association with three risk zones (Low-risk zone, low intermediate risk zone, and High intermediate-risk zone and above). Bilirubin level at or above high intermediate risk zone (over 75th percentile cutoff value) at 24 and 48 hrs of age was considered a cutoff value to find out the association with significant hyperbilirubinemia at 72 hrs of age.6

Statistical Analysis

Data was entered on the computer using Microsoft Office Excel Software program for Windows, then transferred to the Statistical Package of Social Science Software (SPSS)25.0 program to be statistically analyzed. Comparison between groups was performed using the Mann-Whitney test for quantitative variables, while comparison for qualitative variables was performed using Chi-square or Fisher's exact test. P values less than 0.05 were considered statistically significant.

Results

100 newborns were enrolled in the study and analysed for the association of various demographic, clinical, and laboratory markers for early prediction of significant hyperbilirubinemia in the study cohort. 54% of the newborn were male and 46% were female. 91(91%) newborns included were between 37 to 40 weeks, and 9% were above 40 wk of gestation. 85(85%) were appropriate for gestational age, 12 newborns (12%) were Short for gestational age, and 3 newborns were Large for gestational age. [Table1] Out of 100 newborns 5 newborns (33.33%) developed hyperbilirubinemia above high intermediate zone at 48 hrs while 9(30%) newborns developed subsequently developed hyperbilirubinemia at 72 hrs.

Median values for gestational age and birth weight were 38 weeks, 3.1 kg respectively, in study groups. 12 newborns (12%) showed signs of dehydration and out of these 12 newborns, 7 developed hyperbilirubinemia subsequently at 72 hrs of life. 31% received top feeding or mixed feedings, while 17% newborn first feeding was delayed for more than 3 hrs due to inadequacy of lactation on first few days. [Table2] Maternal age, social status, parity, cesarian section, and oxytocin induction were not associated with hyperbilirubinemia at 72 hrs of life. While Instrumental delivery using vacuums and forceps had significantly higher chances of developing significant NNHB at 72 hrs. ($p<0.05$ [Table1]

We also studied 24 hrs. bilirubin and 48 bilirubin to find out association to significant hyperbilirubinemia. Total bilirubin >6 at 24 hrs. and >11.8 at 48 hrs of life which corresponds to high intermediate risk zone cutoff in Bhutani nomogram, and we found this association to be statistically significant. Gender, gestational age, fetal growth had no statistical differences in the occurrence of NNHB. In our study birth weight <2.5 kg, delayed first feeding, dehydration, and 48 Hr serum bilirubin >11.8 mg/dl were significantly associated with significant hyperbilirubinemia($p<0.05$). [Table2]

Table 1: Demographic risk factors for the association to significant NNHB in term newborn at 72 hrs of life

Variables		Significant NNHB at 72 hrs of age=20	Total	P-value	95 CI	OR
Social status	Middle class	14(17.44%)	72(72%)	0.08	0.39-1.7	0.93
	Lower	6(21.43%)	28(28%)			
Maternal age	25-35	11(16.42%)	67(67%)	0.4	0.4-1.3	0.7
	>35	9(27.27%)	33(33%)			
Parity	Primi	9(24.32%)	37(37%)	0.5	0.7-2.7	1.4
	Multi	11(17.46%)	63(63%)			
Type of Delivery	Cesarean	7(14.89%)	47(47%)	0.5	0.5-2.1	1
	Normal	5(16.13%	31(31%)			
	Instrumental	8(36.36%)	22(22%)	0.001	1.7-6.5	3.4
Oxytocin induction	yes	11(18.64%	59(59%)	0.49	0.4-1.4	0.8
	No	9(21.95%)	41(41%)			
Instrumental delivery using vacuums and forceps had significantly higher chances of developing significant NNHB at 72 hrs of age ($p<0.05$)						

Table 2: Neonatal risk factors for association to significant hyperbilirubinemia in term newborn at 72 hrs

Variables		Significant NNHB at 72 hrs of age	Total (%)	P-value	95 CI	OR
Gender	Male	11(20.37%)	54(54%)	0.5	0.6-2.1	1.06
	Female	9(19.56%)	46(46%)			
Birth weight	2-2.5	5(33.33%)	15(15%)	0.01	1.6-4.3	2.3
	>2.5	11(20.37%)	54(54%)			
	>3.5	4(12.90%)	31(31%)			
Gestational age	37-40	17(18.69%)	91(91%)	0.7	0.5-2.3	0.8
	>40	3(20%)	9(9%)			
Fetal growth	SGA	3(25%)	12(12%)	0.96	0.6-2.2	1.1
	LGA	1(33.33%)	3(3%)			
	AGA	16(18.82%)	85(85%)			
Dehydration	yes	4(33.33%)	12(12%)	0.057	1.06-3.9	2.04
	No	16(18.18%)	88(88%)			
Delayed First feeding (>3 hrs)	Yes	10(29.41%)	17(17%)	0.03	1.18-4.4	2.2
	No	10(12.05%)	83(83%)			
Top feeding/mixed feeding	Yes	9(29.03%)	31(31%)	0.07	1.08-4.26	2.1
	No	11(15.94%)	69(69%)			
24 hr serum bilirubin*	>6 mg/dl	5(33.33%)	15(15%)	0.037	1.18-3.1	2.1
48 hr serum bilirubin*	>11mg /dl	9(30%)	30(30%)	0.001	1.8-7.5	3.6

*24 Hr serum bilirubin >6 corresponds to low intermediate zone and 48 Hr serum bilirubin >11.8 to high intermediate risk zone in Bhutani nomogram birth weight <2.5 kg, delayed first feeding, dehydration,24 Hr serum bilirubin >6mg/dl and 48 Hr serum bilirubin >11.8 mg/dl were significantly associated with significant hyperbilirubinemia ($p<0.05$)

Discussion

Neonatal Hyperbilirubinemia is the most common physical abnormality in newborns. It occurs in about 60-70% of full-term and 80% of preterm newborns. It is also the most common cause of readmission to the hospital during the early neonatal period. Approximately 4% of term neonates readmitted during their first week of life, 85% have jaundice.7

Reliable prediction of at-risk neonates may allow clinicians to plan early discharge of low-risk neonates and timely follow-up of high-risk neonates. Simple, non-invasive, and cost-effective methods should be used in high-risk neonates. Recently various new strategies are being adopted to predict significant Hyperbilirubinemia in these newborns to facilitate early discharge and timely follow-up.6,8 But many of these methods are costly and require repeated sampling and close assessment, which sometimes is not practical in a busy government setting handling large numbers of newborns. Several demographic and clinical factors are described in a recent meta-analysis of available studies in low

resource settings to exacerbate physiological Hyperbilirubinemia and make these newborns more likely to develop severe hyperbilirubinemia complications. In addition, according to some recent studies, even newborns having moderate Hyperbilirubinemia may show minor or subtle neurological abnormality at a later age.

Out of 100 newborns, five newborns (33.33%) developed Hyperbilirubinemia above the high intermediate zone at 48 hrs, while 9(30%) newborns developed subsequently developed Hyperbilirubinemia at 72 hrs. Total bilirubin >6mg/dl at 24 and >11mg/dl at 48 hrs of life corresponds to high intermediate risk zone cutoff in Bhutani nomogram and found this association to be statistically significant. In our study, birth weight <2.5 kg, delayed first feeding, dehydration, 24 and 48-hour serum bilirubin >11 mg/dl were significantly associated with significant Hyperbilirubinemia ($p<0.05$)

In various studies, maternal age, social background, and primiparity are described as risk factors.9-11 Adebami O et al. nine found in their study that social background and advanced maternal age were significant risk factors for the development of severe Hyperbilirubinemia among Term newborns. While Chawla D et al.10 concluded in a large cohort of 743 Indian newborns that newborns of primi mothers were more likely to develop significant Hyperbilirubinemia. Olusanya BO et al.11 did not find these risk factors significant in their observation. We also did not find statistical significance for social background, maternal age, and Parity of mother as a risk factor for Hyperbilirubinemia.

Some newborns may suffer from caloric deprivation during the first week of life due to low volume of feeds and delayed enteral feeding. This condition will lead to decreased gastrointestinal activity, decreased stool frequency, delayed meconium passage, further increased enterohepatic recirculation of bilirubin. In addition, low oral intake may induce a state of fasting in these newborns. Fasting is known to increase enterohepatic circulation by suppressing gastrointestinal motility.12,13 Early initiation of feeding and intervals < 3 hours are related to lower bilirubin levels in a study by M. Alex et al.14 Dehydration or weightless >10% in the first week, Delayed feeding, and mixed feeding was significantly associated with significant Hyperbilirubinemia in a few studies.14-16 We did not find any statistical significance of exclusive breastfeeding in developing significant Hyperbilirubinemia as inadequate breastfeeding is more likely to cause significant hyperbilirubinemia than breastfeeding due to resemblance to fasting state increased enterohepatic recirculation.

On the other hand, dehydration and delayed initiation feeding were significant risk factors in our study causing weight loss ($\geqslant$10%) after birth which can be associated with insufficient oral intake during the first week of life. Studies by M. Alex et al.14, Bilgin et al.15, and Tiwari et al.16 also supported our observations. We observed delayed enteral feeding to be significantly associated with increased risk of Hyperbilirubinemia at 48 and 72 hrs. Bhutani nomogram also identified delayed initiation of feeding as a risk factor for high intermediate risk zone.6 Mixed feeding frequency in our study population was found as high as 31%. As our hospital is tertiary care has high caesarean sections leading to further delay in initiation of breastfeeding, and prolonged separation leads to poor lactation in mothers. However, we did not find mixed feeding to increase the risk of Hyperbilirubinemia in newborns independently. Our results were supported by other studies.15,16

Delivery mode and anaesthesia during the caesarean section may also influence the hyperbilirubinemia risk in new-borns. R.

Gale et al. reported lower bilirubin levels after caesarean, probably explained by placental transfusion or timing of cord clamping.17 We did not observe a statistically significant difference between the caesarean section and newborns born vaginally. Several other studies comparing caesarean section and vaginal delivery also did not find the mode of delivery significant in increasing hyperbilirubinemia risk.15,18,19 Oxytocin induction was also not associated with significant Hyperbilirubinemia in newborns in the present study by a recent study by S. Alkane et al.20 with large sample size.

The present study found that a higher TSB value at 24 & 48 hours is associated with a risk of significant Hyperbilirubinemia at 72 hrs. Bhutani et al. in their study of 2840 term & near term neonates, found that with TSB value >6 mg/dl at 24 and >11 at 48hrs (high intermediate risk zone in hour specific nomogram) were associated with significant Hyperbilirubinemia in at-risk babies with 20% positive predictive value, 91% sensitivity and 86% specificity.6 However, they also included near-term newborns in their study and defined *prematurity* as a risk factor in a high intermediate and low intermediate risk zone. In contrast, our study population has consisted of full-term newborns only, and more than 69% were exclusively breastfed, making our results more comparable to Indian newborns. A study by Randhev S et al.20 with 228 full-term new-borns concluded that 24±6-hour TSB value >6.4 mg/dl had a significant correlation with hyperbilirubinemia development with 87.5% sensitivity,97.9% Negative predictive value, and 80.1% specialty.

Alpay et al.21 and Agarwal, Deorari et al.22 also found that a bilirubin level of >6 mg/dL during the first 24 h of life had a significant association with Hyperbilirubinemia with >90% sensitivity and an NPV. Some studies on Indian new-borns even recommended serum bilirubin level >4.4 at 24 and >6.5 mg per dl at 48 hrs to successfully predict significant Hyperbilirubinemia for Indian new-borns with a similar demographic profile present study.23

Conclusion

The present study concluded that healthy full-term newborn with birth weight <2.5 kg, higher 24 hour and 48-hour serum bilirubin were more likely to experience signify Hyperbilirubinemianemia and often discharged from hospital early.

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