E-ISSN:2349-3267
P-ISSN:2349-5499
Research Article
Indicator

Pediatric Review - International Journal of Pediatric Research
2021 Volume 8 Number 3 May-June

Publisher
MEDRESEARCH
www.medresearch.in

The early indicator of significant hyperbilirubinemia in healthy full-term infants at 72 hrs of age: A prospective cohort study

Arya S.[1], Prajapati J.[2*], Panwar C.[3]

DOI: https://doi.org/10.17511/ijpr.2021.i03.02

[1] Sunil Arya, Associate professor, Department of Pediatrics, M.G.M. Medical College, Indore, Madhya Pradesh, India.

[2*] Jyoti Prajapati, Assistant professor, Department of Pediatrics, M.G.M. Medical College, Indore, Madhya Pradesh, India.

[3] Chetan Panwar, Resident, Department of Pediatrics, M.G.M. Medical College, Indore, Madhya Pradesh, India.

Introduction Hyperbilirubinaemia is a very common and frequently benign condition in newborns, but is a leading cause of hospitalisation in the first week of life. Many healthy full-term newborns develop significant hyperbilirubinemia, often leading to serious complications as bilirubin encephalopathy and death. The present study was aimed to determine early predators and risk factors in full-term healthy newborns developing significant hyperbilirubinemia. **Methods -** This was a prospective observational cohort study conducted at the department of pediatrics at a tertiary care teaching hospital over 1 year enrolling 200 full-term healthy newborns and following them from birth to 72 hrs of life to determine early predictors of hyperbilirubinemia. The data were analysed using the Statistical Package of Social Science Software (SPSS) program. Bilirubin levels measured at 72 hrs were compared to identify significant hyperbilirubinemia using cut off at or above high intermediate risk zone in Bhutani nomogram. **Results-** Neonates with birth weight <2.5 kg, born through instrumental delivery, delayed feeding, dehydration, 24 Hr serum bilirubin >6mg/dl and 48 Hr serum bilirubin >11 mg/dl were significantly associated with significant hyperbilirubinemia($p<0.05$) **Conclusion-** These risk factors can be used as risk indicator to predict the development of significant hyperbilirubinemia in such newborns and better pre-discharge counselling and followup can be ensured in such newborns especially in resource-limited settings.

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

Corresponding Author

Jyoti Prajapati, Assistant professor, Department of Pediatrics, M.G.M. Medical College, Indore, Madhya Pradesh, India.
Email: drjyotimdpedia108@gmail.com

How to Cite this Article

Arya S, Prajapati J, Panwar C. The early indicator of significant hyperbilirubinemia in healthy full-term infants at 72 hrs of age: A prospective cohort study. Pediatric Rev Int J Pediatr Res. 2021;8(3):130-136. Available From https://pediatrics.medresearch.in/index.php/ijpr/article/view/658

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Manuscript Received	Review Round 1	Review Round 2	Review Round 3	Accepted
2021-02-12	2021-02-22	2021-02-28	2021-02-08	2021-02-16

Conflict of Interest	Funding	Ethical Approval	Plagiarism X-checker	Note
No	Nil	Yes	7%	

Introduction

Hyperbilirubinemia is a very common and frequently benign condition in newborns but a leading cause of hospitalisation and readmission in the first week of life. When the total serum bilirubin (TSB) rises above the high-risk zone during the first week of life, it is considered hyperbilirubinemia Nearly 8% to 11% of newborns develop significant hyperbilirubinemia. Neonatal hyperbilirubinemia accounted for 13 deaths per 1000 live births globally and ranked seventh leading cause among all causes of neonatal mortality in the first week of life.[1]. In some newborns, this can cause severe complications progressing to acute bilirubin encephalopathy and kernicterus with a high risk of neonatal mortality and long-term neurodevelopmental impairments. Severe hyperbilirubinemia and its sequelae put a disproportionately high burden in low-income and middle-income countries, primarily due to delays in timely identification and providing effective treatments. [2]. Early detection and treatment of significant hyperbilirubinemia may prevent complications. According to some studies, even moderate hyperbilirubinemia is found to be associated with an increased risk of minor neurologic dysfunction in the first year of life which is often considered safe.[3].

According to the American Academy of pediatrics, healthy newborns discharged within 48 hours of age should have a follow-up visit after 48 to 72 hours for any significant hyperbilirubinemia and other problems.[4]. However, this proposition is difficult in resource-limited settings, as a large number of newborns discharges before 48 hrs residing at a farther distance from the hospital may not come for follow-up. Several non-hemolytic prenatal, natal, and postnatal clinical risk factors as, the previous child with jaundice or treatment with phototherapy, Maternal hypertension, diabetes mellitus. Maternal age >25 years, instrumental delivery, delayed feeding, Suboptimal lactation, dehydration, oxytocin induction, Birth trauma, Maternal medications that could act as triggers in infants with G6PD deficiency or impair bilirubin-albumin binding, large for gestational age and Birth weight >3.5 kg are reported in the literature for healthy full-term newborns. These studies suggest that developing countries share a huge burden on newborns with severe hyperbilirubinemia as compared to high-income countries. [1,2,5,6,7].

Hence we aimed to identify early maternal and neonatal low-cost risk indicators to predict the development of significant hyperbilirubinemia, which will help clinicians to prevent and decrease the incidence of bilirubin induced neurological dysfunction and mortality, especially in resource-limited settings.

Material and Methods

Setting: This was a prospective observational cohort hospital-based study involving 200 consecutive full-term healthy newborns after taking the approval from the institutional ethics committee and informed parents consent over 1 year in a tertiary care teaching hospital.

Inclusion criteria: Full-term newborns delivered at MY 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 haemolytic anaemias (Rh, ABO incompatibility), Neonatal sepsis.

Method: A sample size of 167 was calculated using EpiInfo software by the Kelsey method at a confidence limit of 80%, with an estimated prevalence of 15%, with a margin of error of 5%. 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 collection of the sample by Diazotized sulfanilic test. Various demographic and clinical variables as socio-economic background, gender, delivery mode, drugs given to mother, maternal risk factors, birth weights, anthropometry, a first feeding, dehydration, and feeding pattern were studied for possible contribution in development of hyperbilirubinemia in such newborns developing significant hyperbilirubinemia.

Bilirubin levels were analysed to find out association with 3 risk zone according to the Bhutani nomogram (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. [8].

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) program to be statistically analysed. 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

200 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. 55.5% of the newborn were male and 45.5% were female. 185(92%) newborns included were between 37 to 40 weeks, and 7.5% were above 40 wk of gestation. 173(86%) were appropriate for gestational age, 22 newborns (11%) were Short for gestational age, and 5 newborns were Large for gestational age. [Table1] Out of 200 newborns 19 newborns (33.5%) developed hyperbilirubinemia above high intermediate zone at 48 hrs while 40(9%) 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. 22 newborns (11%) showed signs of dehydration and out of these 22 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 >11.7 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 >11.7 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	Total	P-value	95 CI	OR
Social status	Middle class	28(19%)	146(73%)	0.07	0.38-1.7	0.83
	Lower	12(22%)	54(27%)			
Maternal age	25-35	24(18%)	137(68.%)	0.3	0.3-1.3	0.6
	>35	16(25%)	63(31.5%)			
Parity	Primi	17(23%)	72(36%)	0.4	0.6-2.7	1.3
	Multi	23(18%)	128(64%)			
Type of Delivery	Cesarian	14(15%)	93(46.5%)	0.5	0.4-2.1	1
	Normal	10(15%	64(32%)			
	Instrumental	16(37.2%)	43(21.5%)	0.001	1.6-6.5	3.3
Oxytocin induction	yes	22(18.1%	121(60.5%)	0.48	0.3-1.4	0.7
	No	18(22.7%)	79(39.5%)			
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	23(20%)	111(55.5%)	0.5	0.5-2.1	1.06
	Female	17(19.1%)	89(44.5%)			
Birth weight	2-2.5	12(38%)	31(15.5%)	0.01	1.2-4.3	2.3
	>2.5	19(21%)	111(55.5%)			
	>3.5	9(15.5%)	58(29%)			
Gestational age	37-40	37(20%)	185(92%)	0.6	0.4-2.3	0.8
	>40	3(20%)	15(7.5%)			
Fetal growth	SGA	5(22%)	22(11%)	0.86	0.5-2.2	1.1
	LGA	1(20%)	5(3%)			
	AGA	34(19.6%)	173(86%)			
Dehydration	yes	7(31%)	22(11%)	0.047	1.05-3.9	2.04
	No	33(19%)	178(89%)			
Delayed First feeding(>3 hrs)	Yes	11(32.4%)	34(17%)	0.02	1.17-4.4	2.2
	No	29(17.4%)	166(83%)			
Top feeding/mixed feeding	Yes	18(29%)	62(31%)	0.06	1.07-4.26	2.1
	No	22(15.9%)	138(69%)			
24 hr serum bilirubin*	>6 mg/dl	11(35%)	31(15.5%)	0.027	1.13-3.1	2.1
48 hr serum bilirubin*	>11mg /dl	19(33.5%)	56(28%)	0.001	1.7-7.5	3.6

*24 Hr serum bilirubin >6 corresponds to low intermediate zone and 48 Hr serum bilirubin >11.7 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 >11.7 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 who are readmitted during their first week of life, 85% have jaundice.[9].

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 facilitated early discharge and timely follow-up. [1,8,10]. 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 complications of severe hyperbilirubinemia. [2]

According to some recent studies, even newborns having moderate hyperbilirubinemia may show minor or subtle neurological abnormality at a later age.[3].

Out of 200 newborns, 19 newborns (33.5%) developed hyperbilirubinemia above the high intermediate zone at 48 hrs while 40(9%) newborns developed subsequently developed hyperbilirubinemia at 72 hrs. Total bilirubin >6mg/dl at 24 and >11mg/dl at 48 hrs of life which 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 ($p<0.05$)

Maternal age, social background, and primiparity are described as risk factors in various studies [11,12,13]. Adebami O et al. [11]. 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 [12]. 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 [13]. did not find these risk factors to be significant in their observation. We also did not found statistical significance for social background, and maternal age, and Parity of mother as a risk factor for hyperbilirubinemia.

During the first week of life, some newborns may suffer from caloric deprivation 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 increasing enterohepatic recirculation of bilirubin. Low oral intake may induce a state of fasting in these newborns. Fasting is known to increase enterohepatic circulation by suppressing gastrointestinal motility. [14,15]. Early initiation of feeding and intervals < 3 hours are related to lower bilirubin levels in a study by M. Alex et al. [16].

Dehydration or weightless >10% in the first week, Delayed feeding, and mixed feeding was significantly associated with significant Hyperbilirubinemia in few studies. [14,16,17,18]. We did not find any statistical significance of exclusive breastfeeding in developing significant hyperbilirubinemia. As inadequate breastfeeding is more likely to cause significant hyperbilirubinemia rather than breastfeeding due to resemblance to fasting state and increased enterohepatic recirculation.

On the other hand, dehydration and delayed initiation feeding were a significant risk factors in our study causing weight loss (⩾10%) after birth which can be associated with insufficient oral intake during the first week of life. Studies by M. Alex et al. [16], Bilgin et al [17]. and Tiwari et al. [18]. 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.[8].

Mixed feeding frequency in our study population was found as high as 31.6%. As our hospital is tertiary care has high rates of cesarian 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. [17,18].

Delivery mode and anaesthesia during the cesarian section may also influence the hyperbilirubinemia risk in newborns. R. Gale et al. reported lower bilirubin levels after cesarian probably explained by placental transfusion or timing of cord clamping [19]. We did not observe a statistically significant difference between the cesarian section and newborns born vaginally. Several other studies comparing cesarian section and vaginal delivery also did not found the mode of delivery to be significant in increasing hyperbilirubinemia risk [17,20,21]. Oxytocin induction was also not found to be associated with significant hyperbilirubinemia in newborns in the present study by a recent study by S. Alkane et al. [21]. with a 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 21% positive predictive value, 90% sensitivity and 85% specificity.[8].

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, while our study population has consisted of full-term newborns only, and more than 70% were exclusively breastfed, making our results more comparable to Indian newborns. A study by Randhev S et al. [22]. with 228 full-term newborns concluded that 24±6 hour TSB value >6.4 mg/dl had a significant correlation with the development of hyperbilirubinemia with 87.5% sensitivity,97.9% Negative predictive value, and 80.1% speciality.

Alpay et al. [23]. and Agarwal, Deorari et al. [24]. 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 newborns 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 newborns with a similar demographic profile as in the present study.[25].

There are a few limitations in our study as we could not follow our patients after 72 hrs and did not included readmission data.

Maximum serum bilirubin concentration can be observed till 96 hrs, and newborns in the study population might have developed hyperbilirubinemia after discharge from hospital, and most of these failed to come at follow-up due to their parent rural residence. More studies with a large sample size are needed to be done on Indian full-term healthy newborns before our conclusions can be generalized. The strength of the study is that we evaluated the risk of hyperbilirubinemia using the Bhutani nomogram as a cutoff limit of high intermediate risk zone, making our results more reliable and accurate for healthy term newborns as early as 24 hrs, who are at risk of developing subsequent hyperbilirubinemia.

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. Our study also demonstrated that delayed feeding and dehydration put these newborns at high risk for hyperbilirubinemia. Efforts should be made to implement early feeding and proper counselling during the hospital stay to improve newborn feeding practices to avoid complications of hyperbilirubinemia.

What does the study add to the existing knowledge

Risk factors as low birth delayed feeding, dehydration, higher 24 and 48 bilirubin level>6 and >11 mg /dl are significantly associated with hyperbilirubinemia in healthy full-term newborns.

Author's contribution

Dr Sunil Arya-Concept, study design, data analysis, Final approval of the manuscript, Dr Jyoti Prajapati-Manuscript preparation, data analysis, statistical analysis, Review of Literature, Dr Chetan Panwar-Wrote study protocol, data collection, data analysis, statistical analysis

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