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Original Research Article

Utility of cord blood bilirubin as a predictors of significant neonatal Hyperbilirubinemia in healthy term neonate

Rajkumar M. Meshram, Saira Merchant, Swapnil D. Bhongade*, Sartajbegam N. Pathan

Department of Paediatrics, Government Medical College, Nagpur, Maharashtra, India

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***Correspondence:**
Dr Swapnil D. Bhongade,
E-mail: bswapnil1909@gmail.com

ABSTRACT

Background: Clinical jaundice is evident in more than two-third neonates in their early neonatal life. Early identification of neonates at risk might allow early intervention and prevent complication. Objective of the study was to assess the cord blood bilirubin level as a tool to screen the risk of development of subsequent significant neonatal hyperbilirubinemia in term neonates.
Methods: A prospective observational study was conducted over a period of 2 years on 1040 healthy term neonates. Demographic profile, relevant maternal and neonatal information were recorded. Measurement of cord blood bilirubin, blood group/Rh typing and serum bilirubin at the end of 24 & 72 hours was done to predict significant hyperbilirubinemia.
Results: Incidence of significant hyperbilirubinemia was 11.53%. Gender, gestational age, mode of delivery and birth weight had no correlation with development of significant jaundice. 800 (76.93%) neonates had cord blood bilirubin level ≤3.0mg/dl and 240 (23.07%) neonate had cord blood bilirubin level >3.0mg/dl. Out of 240 (23.07%) neonates with higher cord bilirubin (>3.0 mg/dl), 108 (45%) had significant hyperbilirubinemia at the end of 24 hours with sensitivity 90.00%, specificity 85.65%, positive predictive value 45.00% and negative predictive value 98.50% while 110 (45.83%) neonates were observed with serum bilirubin >17mg/dl at the end of 72 hours with cord blood bilirubin >3mg/dl with sensitivity 91.67%, specificity 84.52% positive predictive value 45.83% and negative predictive value-98.61% and this difference was statistically significant.
Conclusions: Neonates with cord blood bilirubin level ≤3mg/dl can be safely discharged early whereas neonates with bilirubin >3mg/dl will need close follow up to check for development of subsequent significant jaundice. Hence cord blood bilirubin levels help to determine and predict the possibility of significant jaundice among healthy term neonates.

Keywords: Cord blood bilirubin, Icterus, Jaundice, Significant hyperbilirubinemia

INTRODUCTION

Jaundice is the commonest clinical condition in neonate encountered by the pediatrician. Difference between true jaundice and the yellowish tinge in neonate was first time reported by Junker in 18th century.[1] Approximately 60% of full term, 80% of preterm and 3-5% of healthy term neonates develop jaundice in early neonatal life.[2,3] Relative polycythemia, shortened erythrocyte life span, immature hepatic intake and conjugation process along with increased enterohepatic circulation are the common factors responsible for hyperbilirubinemia in term neonate.[4] Though, bilirubin acts as an antioxidant, elevation of unconjugated bilirubin are potentially

neurotoxic and may lead to complication such as bilirubin encephalopathy and kernicterus. Such sequelae could be serious, leading to long term morbidity as patients may develop cerebral palsy, sensoryneural deafness and mental subnormality.

Current practice in neonatology is early discharge of healthy term neonate due to medical, social and economic reason but these neonate required readmission for hyperbilirubinemia.[5] So, The American Academy of pediatrics (AAP) recommends that those neonates discharged within 48 hours should have a follow up visit after 2-3 days to detect significant jaundice and other problems.[6] But such recommendation is not practical in developing countries due to limited follow up facilities.

Physical examination is unreliable to measure serum bilirubin. Under such circumstances it is important to predict the risk of hyperbilirubinemia in order to implement early treatment and minimize their devasting complication. By predicting the neonates likely to develop significant neonatal jaundice early at birth, we can design and implement the follow-up programme in these high risk group effectively. End tidal carbon monoxide measurement, predischarge serum bilirubin/ transcutaneous bilirubin level, predischarge risk assessment and umbilical cord bilirubin level are the various ways to predict postnatal hyperbilirubinemia.[7-10] Though, the diagnostic value of cord bilirubin measurement to predict postnatal hyperbilirubinemia is controversial, estimation of cord bilirubin is practical, cheap and noninvasive.[11] Hence, the purpose of the study was to verify whether the bilirubin levels in cord blood could predict the subsequent development of significant hyperbilirubinemia requiring interventions like phototherapy or exchange transfusion.

METHODS

This prospective observational study was undertaken at neonatology unit of one of the largest tertiary care teaching government referral hospital that provide care to underprivileged, socioeconomically deprived population of central India over a period of 2 year from October 2015 to September 2017. Study was approved by Institutional Ethics Committee. Information obtained during the study was kept confidential. Sample size was calculated by considering prevalence of development of jaundice in term neonate (60%) with precision of 5%, and the confidence level at 95% was 1.96. After explaining the nature and conduct of study in local language and written informed consent from parents or care giver a 1040 healthy term neonate who fulfilled the inclusion criteria were recruited for the study.

Inclusion criteria

- Subsequently born of either sex, delivered vaginally or caesarean section
- Healthy, Full term (gestational age 37 weeks or more)
- Birth weight more than 2.5kg
- Apgar score ≥7 at first and 10 at fifth minute were enrolled in the study

Exclusion criteria

- Neonates with ABO/Rh incompatibility
- Prematurity (gestational age <37 weeks)
- Birth trauma, Cephalhematoma, multiple bruise
- Meconium stained amniotic fluid,
- Early onset sepsis
- Major congenital malformations were excluded from the study

Demographic profile, relevant maternal and neonatal information were recorded in specially designed structured proforma for this study. Gestational age was assessed by New Ballard score.[12] All the neonates were examined daily for feeding pattern, developmental of icterus, passage of adequate stool & urine, lethargy and other danger signs. All the babies were followed up daily for first 3 postnatal days and babies were assessed daily for neonatal hyperbilirubinemia and its severity by Kramer's staging scale.[13]

All neonates were subjected to serum bilirubin estimation, blood group and Rh typing. Blood group estimation was done by using commercially available antisera kit. Serum bilirubin estimation was done by Diazotized sulfanilic acid test on umbilical cord blood which was taken at the time of delivery and at the end of 24 hours and 72 hours of life. Cord serum bilirubin of 3mg/dl was considered as a cutoff value for this study. As per the National neonatology forum and American Academy of Paediatrics guidelines, total serum bilirubin>10 mg/dl at the end of 24 hours of life and ≥17mg/dl at the end of 72 hours of life were considered as significant hyperbilirubinemia.[6]

Those neonates, who developed significant hyperbilirubinemia, were treated with phototherapy. Exchange transfusion was done in neonates, whose hyperbilirubinemia did not respond to phototherapy or crossed the recommended level.

Statistical analysis

The data was entered into Microsoft excel sheet and analysis was done by using software STATA version 14 with "t" test, chi-squre test. Sensitivity, specificity, negative and positive predictive value of test was calculated.

RESULTS

A total of 1040 term neonates were enrolled. A male to female ratio was 1.4:1. Mean birth weight was 2.95±0.16

kg, and a 596 (57.32%) were falling in birth weight 2.5-3kg group, 430 (41.31%) in 3.1-3.5kg group and 14 (1.37%) were >3.5kg. A total of 64.62% mothers were primipara and 60.54% neonates were born by vaginal route. 47.12% mother had A^+ blood group followed by B^+ in 34.04% while commonest blood group of baby was B^+ (35.30%) followed by O^+ in 32.60% (Figure 1).

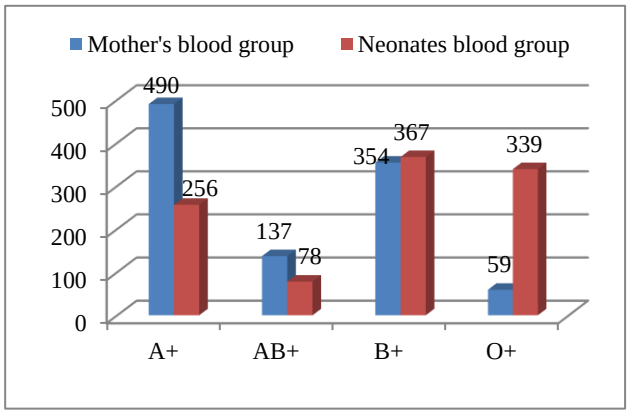

Figure 1: Distribution of maternal and neonatal blood group in study population.

Clinically, in majority of cases 790 (57.97%) jaundice was seen over face, followed by chest and upper abdomen in 152 (14.64%) at the end of 24 hours of life while in 112 (10.77%) jaundice was seen over arms & lower legs, and in 2 (0.19%) neonates jaundice extended up to palms and soles at the end of 72 hours of life (Table 1). 120 (11.53%) neonates had developed significant hyperbilirubinemia and required phototherapy while 2 of them did not respond to phototherapy and needed exchange transfusion. 800 (76.93%) neonates had cord blood bilirubin level ≤3.0mg/dl and 240 (23.07%) neonates had cord blood bilirubin level >3.0mg/dl (Figure 2). Mean cord bilirubin of neonates who developed significant hyperbilirubinemia compared to who did not have significant hyperbilirubinemia was statistically significant. Like wise mean bilirubin level at the end of 24 hours and 72 hours of life was statistically significant in neonates who had significant and non-significant hyperbilirubinemia. (Table 2).

Table 1: Distribution of cases according to Kramer staging.

Kramer staging	At the end of 24 hours	At the end of 72 hours
Face (4-6mg/dl)	790 (75.97%)	540 (51.92%)
Chest and upper abdomen (8-10mg/dl)	152 (14.64%)	266 (25.58%)
Lower abdomen and thigh (12-14mg/dl)	98 (9.39%)	120 (11.54%)
Arms and lower legs (15-18mg/dl)	0	112 (10.77%)
Palms and sole (15-20mg/dl)	0	2 (0.19%)
Total	1040	1040

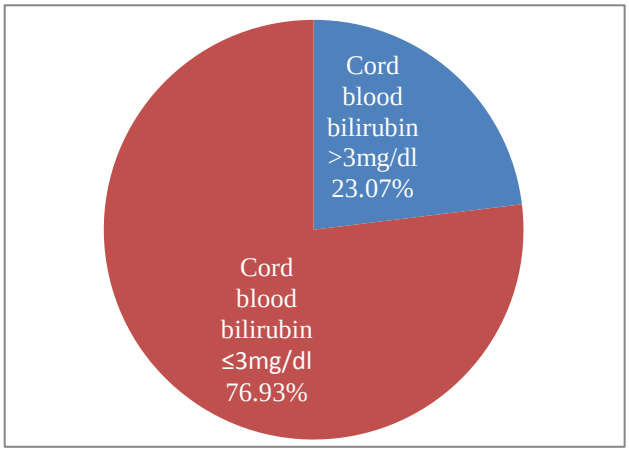

Figure 2: Cord blood bilirubin levels in study population.

Table:2 Distribution of bilirubin level in study population.

Parameter	All Cases (n=1040)	Non-significant hyperbilirubinemia (n=920)	Significant Hyperbilirubinemia (n=120)	Standard error	95% CI	P-value
Cord bilirubin (mean±SD)	2.99±0.79	2.95±0.24	3.32±0.32	0.024	0.32-0.41	<0.0001
Bilirubin level at end of 24 Hours (mean±SD)	5.88±2.36	5.17±1.38	11.27±0.81	0.12	5.84-6.35	<0.0001
Bilirubin level at end of 72 Hours (mean±SD)	9.91±3.97	8.87±2.91	17.68±0.56	0.26	8.28-9.33	<0.0001

Out of 800 (76.93%) neonates with cord bilirubin level ≤3.0mg/dl, 12 (1.50%) had bilirubin more than 10mg/dl at the end of 24 hours while out of 240 (23.07%) neonates with higher cord bilirubin (>3.0 mg/dl), 108 (45%) had total serum bilirubin more than 10 mg/dl at the end of 24 hours with sensitivity 90.00%, specificity

85.65%, positive predictive value 45.00% and negative predictive value 98.50%. Thus, neonates with high cord bilirubin had increased occurrence of significant hyperbilirubinemia at the end of 24 hours and it was statistically significant. (Table 3). 10 (1.25%) neonate had bilirubin >17mg/dl at the end of 72 hours with cord blood bilirubin ≤3mg/dl while 110 (45.83%) neonates were observed with serum bilirubin >17mg/dl at the end of 72 hours with cord blood bilirubin >3mg/dl with sensitivity 91.67%, specificity 84.52% positive predictive value-45.83% and negative predictive value 98.61% and this difference was also statistically significant (Table 4).

Table 3: Correlation between cord blood bilirubin and serum bilirubin at the end of 24 hours.

Cord blood bilirubin	Total Serum Bilirubin at the end of 24 hours		Total (N=1040)	P-value
	>10mg/dl	<10mg/dl		
>3.0mg/dl	108 (45%)	132 (55)	240 (23.07)	<0.001
≤3.0mg/dl	12 (1.50)	788 (98.50%)	800 (76.93)	

Table: 4 Correlation between cord blood bilirubin and serum bilirubin at the end of 72 hours.

Cord blood bilirubin levels	Total serum bilirubin at the end of 72 hours		Total (N=1040)	P-value
	>17mg/dl	<17mg/dl		
>3.0mg/dl	110 (45.83%)	130 (54.17%)	240 (23.07%)	<0.001
≤3.0mg/dl	10 (1.25%)	790 (98.75%)	800 (76.93%)	

DISCUSSION

Clinical jaundice is evident in more than two-third neonates in their early neonatal life. It can occur in healthy term neonate without apparent reason. Although, usually it is a benign postnatal transitional phenomenon, a few neonates had potentially hazardous markedly elevated bilirubin level that can lead to serious complication due to serious brain injury.[14] Current practice of early discharge of healthy term neonate is to provide a home environment/emotional binding with the family members and to decrease nursery overcrowding which in turn to help decrease hospital acquired infection. But these neonates required follow up visit after 48-72 hours to detect hyperbilirubinemia and other problems. Such follow-up facilities are limited in developing countries. Early markers to predict postnatal hyperbilirubinemia is an attractive option to pick up neonate at risk of significant jaundice. So the present study was planned to assess the cord blood bilirubin level as a tool to screen the risk of development of subsequent significant neonatal hyperbilirubinemia in term neonate.

In present study, out of 1040 neonates, 58.50% were male and 41.50% were female. The male to female ratio was 1.4:1 and there were no statistical significance between development of significant hyperbilirubinemia and gender (P=0.2). Similar types of sex distribution are reported in various studies while few studies documented that females outnumbered the number of male.[11,15,16] Amongst 630 neonates delivered vaginally, 63 had significant hyperbilirubinemia while out of 410 caesareans delivered, 57 had significant jaundice and difference between mode of delivery and development of significant hyperbilirubinemia was insignificant(P=0.1). This was in correlation with results of Sun G et al and Ramamoorthy et al.[17,18] Similar to other authors, we could not co-relate birth weight and development of significant hyperbilirubinemia.[15,19] Distribution of blood group of mothers and neonates in study population is similar to observation noted by Taksande et al and there were no significant difference between developments of significant hyperbilirubinemia and blood group of mothers/babies.[20]

In present study, 120 neonates developed significant hyperbilirubinemia, giving prevalence 11.53% which was similar to Jehangir et al, (11.76%) 15 and Pradhan et al, (12.87%) 21, while higher prevalence for development of significant jaundice (29.6%) were reported by Anand K et al, and lower incidence (9.5%) by Taksande et al, and by Hemmati et al, (2.2%).[4,21] All neonates with significant hyperbilirubinemia were treated with phototherapy, two of them did not respond and exchange transfusion was performed on them.

In our study, mean cord bilirubin of those neonates who developed significant hyperbilirubinemia was 3.32±0.32 (mean ±SD) compared to who did not have significant hyperbilirubinemia was 2.95±0.24mg/dl and this difference was statistically significant (P<0.0001). Similarly, mean bilirubin level at the end of 24 hours and 72 hours of life was statistically significant in neonates who had significant and non-significant hyperbilirubinemia. Similar type of differences is reported by various authors.[15,21,22]

It was noted that out of 240 (23.23%) neonate with cord bilirubin level (>3mg/dl), 108 (45%) neonates had significant hyperbilirubinemia at the end of 24 hours with

sensitivity 90.00%, specificity 85.65%, positive predictive value 45.00% and negative predictive value 98.50% , while 110 (45.83%) neonates were observed with serum bilirubin >17mg/dl at the end of 72 hours with sensitivity 91.67%, specificity 84.52% positive predictive value 45.83% and negative predictive value-98.61% and this difference was statistically significant. The probability that a neonates with cord blood bilirubin ≥3.0mg/dl would later become hyperbilirubinemia was 45.83% (positive predictive value), the probability of non-significant hyperbilirubinemia in newborn with cord blood bilirubin ≤3.0mg/dl is 98.61% (negative predictive value). If the neonates become jaundiced, the probability that cord bilirubin was >3.0mg/dl was 91.67 % (sensitivity). Given a non-significant hyperbilirubinemic neonate, the probability that the cord blood bilirubin was ≤3.0mg/dl was 84.52% (specificity). Our findings are supported by various authors (Table 5). Thus, Cord blood bilirubin level appears to be a risk indicator in predicting neonatal hyperbilirubinemia. Cord blood bilirubin level >3.0mg/dl is high risk factor for future development of neonatal hyperbilirubinemia and cord blood bilirubin level <3.0mg/dl is probably safe for early discharge.

Table 5: comparison studies of predictive ability of cord blood bilirubin and the neonatal hyperbilirubinemia.

Studies	Cut off for cord blood bilirubin (mg/dl)	Cut off for neonatal hyperbilirubi-nemia(mg/dl)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Present study	>3	≥17	91.67	84.52	45.83	98.61
Jehangir AB[15] AB (2018)	>3	>16	97.06	99.22	94.29	99.61
Ahire et al[23] (2016)	≥3	≥15	100	98.17	66.67	100
Satrya R et al[24] (2009)	>2.54	≥12.9	90.5	85		
Nahar Z et al[25] (2009)	>2.5	≥17	77%	98.6	91	96
Taksande A et al[20] (2005)	>2	≥17	89.5	85	38.8	98.7
Sehgal P et al[26] (2017)	>2.02	>14	87.50	70.80	39.00	96.50
Khairy et al[27] (2018)	≥1.84	≥15	100	87.1	59.6	100

CONCLUSION

Neonates with cord blood bilirubin level ≤3mg/dl can be safely discharged early whereas neonates with bilirubin levels ≥3mg/dl will need close follow up to check for development of significant jaundice. Hence we recommended that routine estimation of cord blood bilirubin should be emphasized in all term neonates in institutional delivery. It will help to design and implement the follow up programme in high risk group effectively, and to plan early discharge of babies and mothers.

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