International Journal of Contemporary Pediatrics
Shah SK et al. Int J Contemp Pediatr. 2023 Dec;10(12):1771-1777
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20233597

Original Research Article

Association of neonatal hyperbilirubinemia with cord albumin among term appropriate for gestational age neonates

Shweta K. Shah[1]*, Anand K. Jha[1], Satish Sharma[2], Sanjay Gupta[3]

[1]Department of Pediatrics, National Medical College of Medicine, Birgunj, Parsa, Nepal
[2]Department of Pediatrics, Seti Provincial Hospital, Dhangadi, Kailali, Nepal
[3]Pokhariya Hospital, Pokhariya, Parsa, Nepal

Received: 26 October 2023
Revised: 21 November 2023
Accepted: 22 November 2023

***Correspondence:**
Dr. Shweta K. Shah,
E-mail: shweta2044@gmail.com

ABSTRACT

Background: Neonatal hyperbilirubinemia (NH) is the most common abnormality seen during the neonatal period. It affects nearly 60% of term and 80% of preterm neonates during the first week of life. Early discharge of healthy term and late preterm newborns after normal vaginal delivery is a common practice however there are reports of bilirubin induced brain damage (kernicterus) occurring in these infants**.** Therefore, to ascertain whether cord albumin can be used as a reliable indicator for predicting neonatal hyperbilirubinemia.
Methods: A tertiary care hospital-based cross-sectional study was conducted in 142 healthy late preterm and term newborns of either gender with icterus appearing only after 24 hour of life with no other illness using a non-probability sampling method. Data analysis was done using statistical package for the social sciences (SPSS) version 16. Chi-square was used to determine the association between cord albumin and hyperbilirubinemia.
Results: There is a significant negative correlation between cord albumin and serum bilirubin at 72-96 hours of life (p=0.001). A total of 142 healthy late preterm and term neonates included. The study group based on Cord serum albumin (CSA) levels ≤2.8 g/dl, 2.9-3.3 g/dl, and ≥3.4 g/dl shows 77.27%, 22.7% and none respectively developed NH requiring phototherapy. According to receiver operating curve (ROC) analysis, the cutoff point of 2.75 g/dl provides the best sensitivity and specificity result.
Conclusions: Cord serum albumin level ≥3.4 g/dl are probably safe for early discharge whereas cord serum albumin level <3.4 g/dl will need a close follow-up to check for the development of jaundice.

Keywords: Cord serum albumin, Neonatal hyperbilirubinemia, Prediction and newborns

INTRODUCTION

Neonatal jaundice is extremely common as almost every newborn develops an unconjugated serum bilirubin level of more than 1.8 mg/dl during the first seven days of life.[1] Data from the Global Burden of Disease study in 2016 showed that neonatal jaundice accounted for 1309.[2] 3 deaths per 100 000 live births and it was ranked seventh globally among all the neonatal deaths in the early neonatal period (0–6 days).[3,4]

Neonatal jaundice is defined as yellowish discoloration of the skin, sclera of the eyeball, and mucous membrane caused by deposition of bile salts in these tissues.[6-8] Jaundice is observed during the first week of life in approximately 60% of term infants and 80% of preterm infants.[10] In the majority of neonates, unconjugated hyperbilirubinemia reflects a normal physiological phenomenon that is of little consequence. But in some neonates extremely high bilirubin can lead to many complications like ABE and kernicterus.[8]

Early discharge of healthy term and late preterm newborns after normal vaginal delivery has become a common practice, because of medical reasons like prevention of nosocomial infections, social reasons which include an early naming ceremony in the family, and due to economic constraints. However, babies may develop jaundice in this period which may be missed or delay in recognition unless the baby is closely monitored.

There is a concern of the paediatrician regarding the early discharge due to reports of bilirubin-induced brain damage occurring in healthy term infants even without haemolysis. The neurological effect may result in serious conditions like cerebral palsy, sensorineural deafness, and mental retardation.[12]

Early treatment of jaundice with phototherapy is effective, simple, and cheap.

By predicting the newborns developing significant neonatal jaundice early at birth, we can design and implement the follow-up program in high-risk groups effectively and thus prevent kernicterus.[7]

The study aims to determine if umbilical cord serum albumin level is a good predictor for subsequent development and the severity of jaundice in high-risk newborns.

Plasma albumin limits the toxicity of bilirubin by reducing the unbound bilirubin concentration, thereby competing with tissues for bilirubin binding and thus preventing its deposition into the extrahepatic tissues, including sensitive tissue such as brain.

So, by predicting the newborns developing significant neonatal jaundice early at birth, we can design and implement the follow-up program in high-risk groups effectively and if required delay in discharge.

The primary objective of the study is to identify the association and cut off value of cord serum albumin with significant hyperbilirubinemia.

METHODS

This study was conducted in National Medical College Birgunj which represents most population of mid terai area of Nepal on May 2020 – April 2021 after obtaining approval from institutional review committee of National Medical College, Nepal.

It included 142 healthy newborns delivered to our institute during that period. Inclusion criteria were Newborn with gestational age ≥35 to 42 weeks of gestation delivered (normal and C-section) at NMCTH with Apgar more than 7 at 1 min. Rh incompatibility, newborn with gestational age <35 weeks, neonatal sepsis, birth asphyxia, instrumental delivery (forceps and vacuum),respiratory distress, meconium aspiration syndrome, neonatal jaundice within 24 hours, Apgar score less than 7 at 1 min, newborn with severe congenital malformations e.g. Spina bifida, encephalocele, anencephaly, gastroschisis, omphalocele were excluded from the study.

An informed and written consent was obtained from the mothers of the newborn before enrolling them in the study. Demographic profile and relevant information were collected by using structured performa by interviewing the mother and mother's case sheet. Gestational age was assessed by the new Ballard score. The Blood group and CSA level of the baby were estimated at birth. All enrolled babies were followed up for jaundice and clinical assessment for jaundice was done according to Kramer dermal scale.

Once clinically jaundice was observed, blood was sent for total serum bilirubin measurement at 72-96 hours of age and result obtained were compared to the guidelines as per the American Academy of pediatrics practice parameter, 2004. Each case was followed by regular examination and frequent monitoring of total serum bilirubin, to assess the severity of jaundice and response to treatment. Those who did not develop clinically visible jaundice were followed up later on. Early appearances of jaundice before 72 hours with risk factor were excluded.

Cord serum blood (2 ml) was collected from placental side after its separation, centrifuged in plain vial and subjected to investigation Blood group analysis (ABO and Rhesus typing) and cord serum albumin.

Under all aseptic precautions 1 ml of peripheral venous blood was drawn from all the babies enrolled in the study at 72-96 hours of life. Further bilirubin sample was sent if indicated after physical assessment of the babies. Serum bilirubin ≥17 mg/dl after 72 hours of life was taken as hyperbilirubinemia and treatment is advised, as per the American Academy of pediatrics practice parameter, 2004.

The data were entered into Microsoft excel 10 and processed in the statistical package for social sciences (SPSS) software version 16 for Windows. For descriptive statistics mean, standard deviation (SD), percentage, was calculated, and graphical, tabular presentations were tabulated. For inferential statistics in comparing categorical variables Pearson's Chi-square test was used and the odd ratio was calculated at a 95% confidence interval. The level of significance was set at <0.05. ROC analysis was done to find the cutoff value of cord albumin in the detection of hyperbilirubinemia.

Diagnostic values based on area under curve - 0.9-1.0: excellent test, 0.8-0.9: good test, 0.7-0.8: fair test, 0.6-0.7: poor test, and 0.5-0.6: fail

Other metrics of diagnostic utility (sensitivity, specificity, positive predictive value, and negative predictive values) were calculated.

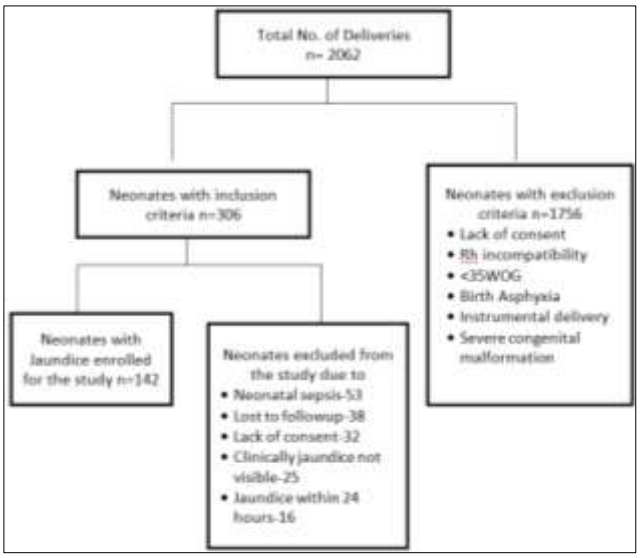

Figure 1: Flow diagram depicting number of cases.

RESULTS

Total number of deliveries conducted during study period from May 2020 to April 2021 in the department of Obstetrics, National Medical College was 2062. However, only 142 neonates fulfilling the selection criteria were enrolled for this study. The various reasons for exclusion of the mother and neonates are depicted in the flow diagram.

The mean maternal age and period of gestation of the baby were 25 years and 38 weeks of gestation respectively. The mean birth weight is 2.84 kg whereas cord serum albumin is 3 g/dl. That majority (57.7%) of newborn was male whereas 42.3% were female, 51.4% of neonates delivered by SVD and 48.6% by LSCS. Neonates delivered mostly in age group 20-29 years and in parity 2. There was history of Oxytocin administration in 57.7% of cases. 15 cases had a history of a previous sibling having NNJ requiring phototherapy. Out of 142,116 neonates belong to birth weight 2.5 to 3. 5 kg. In total 142 cases 15.5% cases received phototherapy for hyperbilirubinemia as given in Table 3.

The Table 7 showed the comparison of the need for phototherapy with different levels of cord serum albumin. P value shows 0.001 which is statistically significant using Chi square test. Thus, it postulated that when there is a fall in cord serum albumin there is a risk of hyperbilirubinemia.

We performed a receiver operating curve (ROC) analysis to test the usefulness of cord albumin as an indicator for predicting neonatal hyperbilirubinemia.

In this study area under the curve (AUC) is 0.771. The sensitivity in the neonates was determined and found to be 72.7%, while specificity was 70%. The positive predictive value was found to be 30.8% and the negative predictive value was found to be 93.3%. The accuracy rate was 70.4%, standard error was found to be 0.051, and the 95% confidence interval lower bound and the upper bound was 0.671 and 0.871 respectively.

According to this result, the cut-off point of 2.75 g/dl provides the best sensitivity and specificity for cord albumin as the indicator for neonatal hyperbilirubinemia.

Table 1: Distribution of the neonates according to socio-demographic factors; maternal age, birth weight, period of gestation, cord albumin and total serum bilirubin (N=142).

Socio-demographic factors	Mean±SD
Maternal age in years	24.84±4.46
Birth weight in kg	2.84±0.42
POG in Weeks	38.22±1.76
Cord Albumin	3.05±0.45
TSB after 72 hours	9.63±4.40
Direct	0.44±0.16
Indirect	9.19±4.33

Table 2: Distribution of the neonates according to socio-demographic factors with variables (N=142).

Socio-demographic factors	No of cases (n)	Percentage
Sex		
Female	82	57.7
Male	60	42.3
Mother blood group		
A positive	27	19
AB positive	13	9.2
B positive	43	30.3
O positive	59	41.5
Mode of delivery		
LSCS	69	48.6
SVD	73	51.4
Oxytocin administration in mothers		
No	60	42.3
Yes	82	57

Table 3: Distribution of the neonates according to socio-demographic factors; cord serum albumin and total serum bilirubin (N=142).

Socio-demographic factors	No of cases (n)	Percentage
Cord serum albumin		
≤2.8	59	41.5
2.9-3.3	53	37.3
≥3.4	30	21.1
Total serum bilirubin		
≤10	96	67.6
10-14	24	16.9
≥17	22	15.5

Table 4: Comparison of gender distribution and CSA level.

Sex	Cord serum albumin level (g/dl) (%)			Total	P value
	≤2.8	2.9-3.3	≥3.4		
Female	36 (61)	30 (56.6)	16 (53.3)	82 (57.7)	0.769
Male	23 (39)	23 (43.4)	14 (46.7)	60 (42.3)	
Total	59 (100)	53 (100)	30 (100)	142 (100)	

Table 5: Comparison of oxytocin administration in mother with cord serum albumin.

Oxytocin administration	Cord serum albumin (g/dl) (%)			Total	P value
	≤2.8	2.9-3.3	≥3.4		
No	26 (44.1)	22 (41.5)	12 (40)	60 (42.3)	0.926
Yes	33 (55.9)	31 (58.5)	18 (60)	82 (57.7)	
Total	59 (100)	53 (100)	30 (100)	142 (100)	

Table 6: Association between genders with hyperbilirubinemia.

Sex	Hyperbilirubinemia (%)		Total	P value
	No	Yes		
Female	66 (55)	16 (72.7)	82	0.122
Male	54 (45)	6 (27.3)	60	
Total	120 (100)	22 (100)	142 (100)	

Table 7: Comparison of hyperbilirubinemia with cord serum albumin.

Hyperbilirubinemia	Cord serum albumin (%)			Total	P value
	≤2.8	2.9-3.3	≥3.4		
No	42 (71.2)	48 (90.6)	30 (100)	120 (84.5)	0.001
Yes	17 (28.8)	5 (9.4)	0	22 (15.5)	
Total	59 (100)	53 (100)	30 (100)	142 (100)	

DISCUSSION

In this study we have found that there is no gender predilection for the development of NH (p=0.122) which was supported by most of the studies.[18,19,26-29,31,33] In this study, study group is uniformly distributed with 60 male and 82 female babies. There is no significant correlation (p=0.122) in the TSB levels and the sex of the newborn. Hence the present study infers that the significant neonatal hyperbilirubinemia (≥17 mg/dl) is independent of the sex of the newborn. The study done by Trivedi et al showed that male babies have a higher incidence of developing NH than female babies. Study group consisted of 605 newborn, 305 male and 300 females. Neonatal hyperbilirubinemia developed in 115 male and 90 females.[13]

In this study, we have found that there is not a significant relationship between neonates who received oxytocin during delivery and neonatal hyperbilirubinemia. Out of 142 neonates, only 82 received oxytocin for induction of labor. NH developed in 11/82 neonates whose mothers' received oxytocin and in 11/60 neonates who didn't. A similar study was done by Kumar et al, in 150 neonates and found that there is no significant difference between oxytocin received during delivery and neonatal hyperbilirubinemia (p=0.603) which was supported by Kumar et al and Ahire et al.[18,33,72]

On the contrary the study conducted by Gupta et al on 789 neonates found that there is an increased chance of causing Neonatal hyperbilirubinemia in neonates whose mother received oxytocin during delivery (p=0.002). The reason for this difference is due to its ability to develop neonatal hyperbilirubinemia by inducing hemolysis.[34]

The incidence of significant hyperbilirubinemia with similar studies showed variable results as studied above. In this study, the incidence of significant hyperbilirubinemia showed 15.5% which is supported by Ahmed et al showed the incidence of significant hyperbilirubinemia as 16%, and Hussain et al show 15.71%.[9,29]

In this study, we have found that there is no significant relationship was found between mode of delivery and hyperbilirubinemia (p=0.433). 73 cases with vaginal delivery 13 developed serum bilirubin ≥17 mg/dl and off 69 cases with caesarean section 9 developed significant hyperbilirubinemia (≥17 mg/dl) which was supported by Sapkota et al.[35] A similar study was done by Reshad et al, Chandan et al, and Chauhan et al, studied between mode of

delivery and hyperbilirubinemia and found no significant relationship.[7,22,27]

In the present study, 142 newborns were included in the study and 22 newborns developed neonatal hyperbilirubinemia. The study group was divided into 3 groups based on the CSA levels ≤2.8 g/dl, 2.9-3.3 g/dl, and ≥3.4 g/dl. In group 1 77.27% (17/22); group 2 22.7% (5/22) and group 3 none developed NH requiring phototherapy. The present study (p<0.001) showed significant correlation between cord albumin and neonatal hyperbilirubinemia which was supported by all studies done at different centre shown in Table 8.

But study done by Sapkota et al in 100 neonates at Nepal Medical College, Nepal found only 5 neonates with significant hyperbilirubinemia. The study showed there is no correlation between cord albumin and hyperbilirubinemia (p value 0.784). This may be due to small sample size of neonates who had bilirubin level ≥17 mg/dl.[35]

ROC analysis to test the usefulness of cord albumin as an indicator for predicting neonatal hyperbilirubinemia showed that CSA is a good predictor of NH with an area under the curve is 0.767.According to our result, the cutoff point of 2.75 g/dl provides the best sensitivity (77.3%) and specificity (70.8%) for cord albumin as the indicator for neonatal hyperbilirubinemia with a positive predictive value of 32.7% and the negative predictive value of 94.4% similar to other studies Aiyappa et al, Hussain et al, and Mishra et al.[16,19,29]

Meshram et al, in their study observed the sensitivity of the cord blood albumin to detect hyperbilirubinemia was 87.50%, while specificity was 84.78% with positive predictive value 42.86% and negative predictive value 98.11%.[25]

Alalfy et al performed a ROC curve analysis to find a cutoff point level of cord blood albumin for development of neonatal hyperbilirubinemia which was 2.75 g/dl; with a sensitivity (64.3%), (81.8%) specificity, PPV (81.8%) and NPV (64.3%).[23]

Hanan et al in their study found that cord serum albumin level of 3.3 g/dl with ROC curve analysis has a sensitivity of (86%) and specificity of (80%), PPV (81%), NPV of (85%) and the accuracy rate was (83%) in predicting neonatal hyperbilirubinemia.[36]

Table 8: Cord albumin level correlation with NH in different studies.

Studies	Year	Total no. of cases	No of cases with NH	Cord albumin level correlation with NH			P value
				Group 1 (CSA level in g/dl)	Group 2 (CSA level in g/dl)	Group 3 (CSA level in g/dl)	
Sahu et al[6]	2011	40	20	14 (≤2.8)	6 (2.9-3.3	0 (≥3.4)	<0.001
Trivedi et al[13]	2013	605	205	120 (<2.8)	59 (2.8-3.5)	26 (>3.5)	<0.05
Meena et al[15]	2015	100	28	18 (<2.8)	9 (2.8-3.8)	1 (>3.8)	<0.001
Reshad et al[7]	2016	75	31	19 (≤2.8)	10 (2.9-3.4)	2 (≥3.4)	0.001
		75	41	33 (≤2.8)	8 (2.9-3.4	0 (≥3.4)	0.001
Kumar et al[18]	2016	100	10	9 (≤2.8)	1 (2.9-3.3)	0 (≥3.4)	0.003
Aiyappa et al[19]	2017	165	35	18 (<2.8)	19 (>2.8)		<0.05
Mishra et al[17]	2018	300	35	33 (≤2.8	2 (2.9–3.3)	0 (≥3.4)	<0.00001
Meshram et al[25]	2018	1040	120	105 (<2.8)	15 (>2.8)		<0.001
Chandan et al[27]	2019	160	12	1 (<3.3)	9 (3.3-3.8)	2 (>3.8)	0.032
Challa et al[28]	2019	100	19	10 (<2.8)	9 (2.8-3.3)	0 (>3.3)	<0.0001
Hasan et al[36]	2020	100	22	16 (<2.8)	6 (2.8-3.3)	0 (>3.3)	<0.001
Kumar et al[30]	2020	150	18	17 (≤2.8)	1 (2.9-3.3)	0 (≥3.4)	<0.001
Present study	2020	142	22	17 (≤2.8)	5 (2.9-3.3)	0 (≥3.4)	<0.001

CSA=cord serum albumin

Bhat et al in their study found that cord serum albumin <2.8 g/dl had a sensitivity of 93.67%, specificity 56.01% with PPV and NPV of 51.57% and 94.65%, respectively.[32]

Hirevenkanagoudar et al, in their study found that cord serum albumin <2.8 g/dl had a sensitivity of 96.5%, specificity 65.5% with PPV and NPV of 32.1% and 99.8% respectively.[31]

Limitation of our study was only healthy late preterm, and term were only included in the study. An early appearance of neonatal hyperbilirubinemia requiring phototherapy was not included in the study. Short study period and data collected from single centre with small sample size which is not representative of all population.

CONCLUSION

Umbilical cord serum albumin level at birth is a good predictor of subsequent development of significant neonatal hyperbilirubinemia. Healthy late preterm and term newborns with umbilical CSA level ≥3.4 g/dl can be safely discharged early whereas those with albumin level <3.4 g/dl will need a close follow-up for evaluation of

jaundice. This is especially of utmost importance in a developing country like ours with very limited resources. Though CSA level is a good predictor of subsequent NH, other early markers like cord bilirubin level should also be taken into consideration to increase the accuracy. Further multicenter studies with a large sample size need to be done to validate our finding.

ACKNOWLEDGEMENTS

Authors would like to thank the members of department of paediatrics National Medical College and Dr. Sanjay Gupta for their valuable support.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Shah SK, Jha AK, Sharma S, Gupta S. Association of neonatal hyperbilirubinemia with cord albumin among term appropriate for gestational age neonates. Int J Contemp Pediatr 2023;10:1771-7.