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Original Article

Paediatrics Section

Comparison of Umbilical Cord blood Bilirubin (UCB) and Bilirubin Albumin Ratio (BAR) in Predicting Neonatal Hyperbilirubinemia: A Prospective Observational Study

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ABSTRACT

Introduction: Hyperbilirubinemia is a commonly encountered medical condition in neonates. It becomes problematic when the levels of bilirubin raises to abnormally high values leading on to neurological problems. Bilirubin Albumin Ratio (BAR) can be used as a prediction tool for subsequent hyperbilirubinemia in neonates thereby helping in early institution of therapy.

Aim: To compare Umbilical Cord blood Bilirubin (UCB) and the BAR in predicting neonatal hyperbilirubinemia.

Materials and Methods: This prospective observational study was conducted in the neonates born at Al-Azhar Medical College, Thodupuzha, Kerala, India, from April 2020 to February 2021. After obtaining clearance from Institute Research Committee and Institute Ethical Committee, 1025 healthy term babies were included in the study. After an informed consent from either of the parent, cord blood was sent for bilirubin, albumin and the blood group estimation. Babies were examined daily for any development of jaundice for five days or till discharge. Venous blood was sent for bilirubin estimation if clinical icterus was noted by Kramer's rule any time after birth or at 72 hours. If hyperbilirubinemia was detected, treatment was instituted. Two cut-offs for UCB-2 and 2.5 mg/dL and two cut-offs for BAR 0.59 and 0.69 were correlated with the neonatal hyperbilirubinemia using Pearson correlation and Chi-square test. The p-value <0.05 was taken as statistically significant. The cut-off values for cord bilirubin and BAR that could predict hyperbilirubinemia was also obtained from Receiver Operating Curve (ROC).

Results: Of the 1025 babies studied, hyperbilirubinemia was detected in 246 babies (24%). Babies with higher UCB and BAR had statistically significant risk of neonatal hyperbilirubinemia. UCB >2 mg/dL and 2.5 mg/dL and BAR 0.59 and 0.69 were found to strongly correlate with the risk of hyperbilirubinemia. Higher the UCB and BAR, higher the risk. On ROC analysis, cut-off points for UCB and BAR were 2 mg/dL and BAR >0.59 respectively. A highly significant correlation was found between UCB and hyperbilirubinemia as well as between BAR and hyperbilirubinemia with a p-value <0.001. Among UCB and BAR, UCB is found to have better sensitivity and specificity than BAR with cut-off 2 mg/dL with better sensitivity of 75.2% and cut-off 2.5 mg/dL with a better specificity of 89.6%.

Conclusion: UCB and BAR are strong predictors of neonatal hyperbilirubinemia with UCB a better predictor than BAR.

Keywords: Cord blood albumin, Neonates, Prediction tool, Umbilical cord bilirubin

INTRODUCTION

Hyperbilirubinemia is a normal physiological phenomenon seen in neonates. It is seen in 80% preterm babies and 60-70% of term babies by day 2 to day 4 [1]. Mean bilirubin levels in cord blood range from 1.4 to 1.9 mg/dL [2,3]. Newborns produce bilirubin at a rate of approximately 6 to 8 mg per kg per day [4]. The average total serum bilirubin level usually peaks at 5 to 6 mg per dL on the third to fourth day of life and then resolves usually by 1-2 weeks of life [5]. Infants with multiple risk factors may develop an exaggerated form of physiologic jaundice in which the total serum bilirubin level may rise as high as 17 mg/dL [6]. Hyperbilirubinemia in neonates is caused mainly due to decreased Red Blood Cell (RBC) survival, increased enterohepatic circulation and transient bilirubin conjugation deficiency [1]. Hyperbilirubinemia if untreated can lead on to kernicterus which is a clinical condition associated with neurodevelopmental delays, seizures and even death [7,8]. Jaundice is considered pathologic if it presents within the first 24 hours after birth, the total serum bilirubin level rises by more than 5 mg/dL per day or is higher than 17 mg/dL, or an infant has signs and symptoms suggestive of serious illness [9]. Liver synthesises albumin by early foetal life [10]. In term babies, the normal range of serum albumin is 3.1±0.3 g/dL and a level of 2.8 mg/dL is considered the lower limit [11]. Albumin makes up 70-75% of plasma oncotic pressure. It helps in the transfer of bilirubin, cysteine, free fatty acids, etc. to different parts of the body. Approximately, 8.5 mg of bilirubin binds to 1 mg of albumin [12]. The binding of bilirubin to albumin helps in reducing the risk of neonatal hyperbilirubinemia. American Academy of Paediatrics (AAPs) recommends all neonates to be screened for hyperbilirubinemia before discharge [13]. AAP also recommends review of all neonates after 48 to 72 hours for the development of jaundice if they are discharged before 72 hours [14].

Various studies have independently assessed the predictive value of cord bilirubin and albumin for neonatal hyperbilirubinemia. There is paucity of studies comparing the predictive values of cord bilirubin and cord BARs for predicting neonatal hyperbilirubunemia. Bhat JA et al., found that cord blood bilirubin/albumin ratio >0.98 can predict hyperbilirubinemia with sensitivity 78.79% and specificity 95.5% [15]. El Mashad GM et al., found out that a cut-off BAR of

0.6 can predict hyperbilirubinemia [16]. This concept of predictability of hyperbilirubinemia offers an excellent option for finding out the babies at risk for jaundice and this will help us in developing a good neonatal protocol especially for resource limited countries like India.

Hence, this study aimed to compare the predictive value of UCB and BAR in predicting the development of subsequent neonatal hyperbilirubinemia.

MATERIALS AND METHODS

This prospective observational study was carried out at the labour room, NICU and postnatal wards, Department of Paediatrics and Neonatology, Al-Azhar Medical College and Super Speciality Hospital, Kerala, India, from April 2020 to February 2021. Approval from the Institute Ethics Committee (IEC) was obtained (AAMC/IEC/2020/07). Overall, 1078 babies were selected for the study. Total 21 babies who had incomplete laboratory records and 32 babies who went against medical advice after 24 hours making them unavailable for serum bilirubin estimation at 72 hours were not included into the study. Thus, finally 1025 healthy term babies were studied.

Inclusion criteria: Term neonates with gestational age >37 weeks of either gender, from either normal vaginal delivery or caesarean section with birthweight ≥2 kg and Apgar score ≥7 at first minute of life were included into the study.

Exclusion criteria: Preterm babies, babies with ABO and Rh incompatibility and whose Apgar score were <7 at first minute of life, babies born by instrumental delivery, neonates with sepsis, respiratory distress and major congenital anomalies were excluded from the study.

After obtaining written informed consent from the parents, relevant antenatal history was obtained by interviewing the mother or from the antenatal records. After delivery of the baby, the umbilical cord was double clamped. Two mL of cord blood was collected in two plain bottles, one vial sent for analysis of baby's blood group and other one for bilirubin and albumin estimation.

Cord bilirubin was assessed by semi-automated analysis using colourimetric diazo method. Umbilical cord albumin was measured using semi-automated bromocresol green method. Baby's blood group was also sent for analysis. Thus, total cord bilirubin, cord albumin and baby's blood group and rhesus was checked for the neonates.

The newborns were examined daily for the development of jaundice for five days or till discharge whichever was earlier. A peripheral venous blood was sent at 72 hours for bilirubin estimation. If clinical icterus was felt by Kramer's rule at any time, venous blood withdrawn and sent for bilirubin assessment. Bilirubin >13 mg/dL on day 2 or ≥17 mg/dL on day 3 were taken as the criterion for phototherapy according to National Neonatology Forum of India (NNF)clinical practice Guidelines [14].

The risk of hyperbilirubinemia was analysed with cord bilirubin cut-off values of and 2 mg/dL and 2.5 mg/dL and BAR of 0.59 and 0.69. ROC curve analysis was also done to get the cut-offs of cord bilirubin and BAR which can predict hyperbilirubuinemia.

STATISTICAL ANALYSIS

The data including baseline characteristics, blood group, cord bilirubin, cord albumin and serum bilirubin at 72 hours were first entered into a proforma and then into an Excel sheet. Data was analysed using Statistical Package for the Social Sciences (SPSS) 16.0. The baseline characteristics of the study group was analysed. The babies with hyperbilirubinemia and babies without hyperbilirubinemia were compared based on their cord bilirubin values and BARs. Two cut-offs for UCB 2 mg/dL and 2.5 mg/dL and two cut-offs for BAR 0.59 and 0.69 were used for analysis. Qualitative data were expressed as number and percentage and quantitative data were expressed as mean±Standard Deviation (SD). The statistical data were analysed with t test, Chi-square test and Pearson's correlation. The p-value ≤0.05 was considered as statistically significant. The ROC curve was constructed and the area under the curve was done to detect the cut-off values of cord bilirubin and BAR.

RESULTS

Of the 1025 babies, 564 (55%) were males and 461 (45%) were females; 132 (12.9%) babies had birth weight between 2-2.5 kg, 788 (76.9%) babies had a birth weight between 2.5-3.5 kg and 105 (10.2%) babies had birth weight more than 3.5 kg. Overall, 710 (69.3%) babies were delivered by normal vaginal delivery, and 315 (30.7%) were delivered by caesarean section. The most common blood group of the babies was O positive seen in 518 (50.6%) babies and the least common blood group was AB negative which was seen in only 2 (0.8) babies. There were no statistically significant differences in the baseline characteristics of babies between those with/without neonatal hyperbilirubinemia [Table/Fig-1].

Neonatal characteristics		Hyperbilirubinemia		p-value (Chi-square test)
		Yes N (%) 246 (24)	No N (%) 779 (76)	
Gender	Male	128 (52)	436 (55.9)	0.157
	Female	118 (48)	343 (44.1)	
Mode of delivery	Vaginal	192 (78)	518 (66.5)	0.16
	Caesarean section	54 (22)	261 (33.5)	
Blood group of the baby	O+	114 (46.3)	404 (51.8)	0.209
	B+	49 (19.9)	145 (18.6)	
	A+	43 (17.4)	139 (17.8)	
	AB+	23 (9.4)	49 (6.4)	
	O-	7 (2.9)	21 (2.7)	
	A -	5 (2)	11 (1.4)	
	B -	3 (1.2)	10 (1.3)	
	AB-	2 (0.8)	0	
Birth weight (kg)	2-2.5	31 (12.6)	101 (13)	0.382
	2.5-3.5	188 (76.4)	600 (77)	
	>3.5	27 (11)	78 (10)	

[Table/Fig-1]: Comparison of baseline characteristics of two groups.

Regarding the clinical and laboratory data, the mean weight of the babies was 2.99±0.44 kg, the mean UCB was 2.09±0.4 mg/dL and the mean BAR was 0.59±0.14.

Among 1025 babies, 246 (24%) had hyperbilirubinemia. They were treated using phototherapy as per protocols. None of the babies required exchange transfusion. Among the babies who had hyperbilirubinemia requiring phototherapy, the mean UCB was 2.41±0.50 mg/dL and the mean cord albumin was 3.69±0.35 mg/dL and the mean BAR was 0.66±0.15.

The correlation between UCB and the risk of development of hyperbilirubinemia was analysed with two cut-off values of UCB-2 mg/dL and 2.5 mg/dL.

Out of 1025 babies, 534 (52.1%) had UCB <2 mg/dL and 491 (47.9%) had UCB >2 mg/dL. Out of 534 babies with UCB <2 mg/dL, only 61 (11.4%) developed hyperbilirubinemia and out of 491 babies with UCB >2 mg/dL, 185 (37.7%) developed hyperbilirubinemia. The sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of UCB 2 mg/dL in predicting the risk of neonatal hyperbilirubinemia were 75.2%, 60.7%, 37.6% and 88.6% respectively. On further analysis with UCB cut-off of 2.5 mg/dL in 1025 babies, 857 (83.6%) babies had UCB <2.5 mg/dL and 168 (16.4%) had UCB >2.5 mg/dL. Out of 857 babies who had UCB <2.5 mg/dL, only 159 (18.6%) developed hyperbilirubinemia whereas 87 (51.8%) developed hyperbilirubinemia among 168 babies with UCB >2.5 mg/dL. The sensitivity, specificity, PPV and NPV with cut-off of UCB >2.5 mg/dL are 35.4%, 89.6%, 51.8% and 81.5%, respectively.

Correlation of UCB cut-off of 2 mg/dL and UCB cut-off of 2.5 mg/dL to predict neonatal hyperbilirubinemia were both highly statistically significant with p-value of <0.001. The raising of cut-off from 2 to 2.5 mg/dL, it was found that the specificity and PPV improved [Table/Fig-2].

Cut-off values	Umbilical Cord Bilirubin (mg/dL) (UCB)	Neonatal hyperbilirubinemia		Total	Chi-square value	p-value
		Present 246 (24)	Absent 779 (76)			
Cut-off 2	>2	185 (37.7)	306 (62.3)	491 (100)	96.67	<0.001
	<2	61 (11.4)	473 (88.6)	534 (100)		
Total		**246 (24)**	**779 (76)**	**1025 (100)**		
Cut-off 2.5	>2.5	87 (51.8)	81 (48.2)	168 (100)	85.05	<0.001
	<2.5	159 (18.6)	698 (81.4)	857 (100)		
Total		**246 (24)**	**779 (76)**	**1025 (100)**		

[Table/Fig-2]: Cross tabulation between cut-off cord bilirubin 2 mg/dL and 2.5 mg/dL and neonatal hyperbilirubinemia.

The mean BAR was found as 0.59±0.14. The risk of hyperbilirubinemia was analysed with a BAR cut-off of 0.59. A total of 160 (36.4%) babies who had BAR >0.59 developed hyperbilirubinemia as compared to 86 (14.7%) babies who had BAR <0.59. That demonstrates that as the BAR level rises, the risk of hyperbilirubinemia increases. There is a statistically significant correlation between BAR 0.59 and hyperbilirubinemia. Cut-off value of BAR at 0.59 had a sensitivity, specificity, PPV and NPV of 65%, 64.2%, 36.4% and 85.3%, respectively. On analysis of the risk of hyperbilirubinemia with a BAR cut-off of 0.69, 84 (46.9%) babies who had BAR >0.69 developed hyperbilirubinemia as compared to 162 (19.1%) babies who had BAR <0.69. Cut-off BAR 0.69 had sensitivity, specificity, PPV, NPV of 43.5%, 80.5%, 41.3% and 81.9%, respectively [Table/Fig-3].

Cut-off values	Bilirubin Albumin Ratio (BAR)	Neonatal hyperbilirubinemia		Total	Chi-square value	p-value
		Present 246 (24)	Absent 779 (76)			
Cut-off 0.59	>0.59	160 (36.4)	279 (63.6)	439 (100)	65.22	<0.001
	<0.59	86 (14.7)	500 (85.3)	586 (100)		
Total		**246 (24)**	**779 (76)**	**1025 (100)**		
Cut-off 0.69	>0.69	84 (46.9)	95 (53.1)	179 (100)	62.50	<0.001
	<0.69	162 (19.1)	684 (80.9)	857 (100)		
Total		**246 (24)**	**779 (76)**	**1025 (100)**		

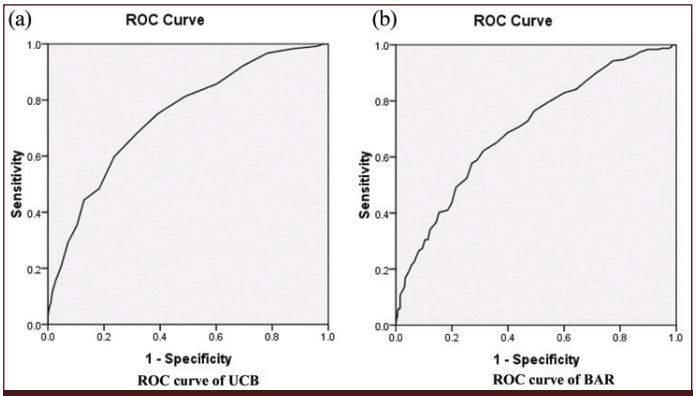
[Table/Fig-3]: Cross tabulation between cut-off Bilirubin Albumin Ratio (BAR) 0.59 and 0.69 and neonatal hyper bilirubinemia.

There was a statistically significant correlation between the BAR and neonatal hyperbilirubinemia with a p-value <0.001 with both BAR cut-offs of 0.59 and 0.69. The raising of cut-off from 0.59 to 0.69, the specificity and PPV improved [Table/Fig-4].

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
UCB >2 mg/dL	75.2	60.7	37.6	88.6
UCB <2.5 mg/dL	35.4	89.6	51.8	81.5
BAR >0.59	65	64.2	36.4	85.3
BAR >0.69	43.5	80.5	41.3	81.9

[Table/Fig-4]: Sensitivity, Specificity, Positive Predictive Value (NPV) Negative Predictive Value (NPV).

A cut-off level of UCB and BAR was found as 2.0 and 0.59 from ROC curve [Table/Fig-5]. The area under the ROC curve of UCB was 0.742 and the area under the ROC curve of BAR was 0.698 of the total area. A p-value of <0.001 suggests the strong statistically significant correlation of both UCB and BAR in predicting neonatal hyperbilirubinemia.



[Table/Fig-5]: ROC curve for depicting: a) Umbilical Cord blood Bilirubin (UCB); b) Bilirubin Albumin Ratio (BAR) for the prediction of neonatal hyperbilirubinaemia.

DISCUSSION

In the present study of 1025 babies, mean birth weight was 2.99±0.44 kg. Majority (76.4%) of babies had birth weight between 2.5 to 3.5 kg. A 69.3% babies were delivered by normal vaginal delivery. Only 30.7% were delivered by caesarean section as compared to 40.4% caesarean births in a private health facility in rural areas according to National Family Health Survey (NHFS)-5 [17]. The birth weight, sex of the baby, mode of delivery and blood group have no statistically significant differences between the babies who developed hyperbilirubinemia or not. The most common blood group seen was O+, found in 518 (50.6%) babies.

The incidence of neonatal hyperbilirubinemia was 24% (246 cases). This was in concordance with the study by Satrya R et al., with reported incidence of hyperbilirubinemia of 24% [18]. There are studies which reported lower incidence of 12.8%, 10.6% than this as well as studies which has reported higher incidence of 34% [19-21]. The difference may be due to various reasons. The studies have been conducted in various geographical locations and in different races. There is difference in the methods used for estimation of bilirubin like diazo method and enzymatic method which uses bilirubin oxidase. Zeitoun AA et al., had included high risk babies and near term babies who increased the incidence of hyperbilirubimemia [21].

Even though there are a few studies which compared the predictive value of UCB and BAR for neonatal hyperbilirubinemia, this study

was one of the largest samples on 1025 babies. Among the babies who had UCB >2 mg/dL, 37.7% (183 out of 491 babies) developed hyperbilirubinemia as against 51.8% (81 out of 168 babies with TCB >2.5 mg/dL), when cut-off of 2.5 mg/dL was used. This implies that, as the cord bilirubin level rises, the risk for hyperbilirubinemia also increases. A highly statistically significant correlation was found between UCB and hyperbilirubinemia with p-value of <0.001. The results are consistent with many studies done in this field [22-26]. Kara L et al., found that umbilical cord blood bilirubin was higher in those neonates who received phototherapy than in those who did not. Hence, they concluded that umbilical cord blood bilirubin may help predict risk for severe hyperbilirubinemia and phototherapy [22]. A previous study done in this centre found that the UCB can predict neonatal hyperbilirubinemia and hence recommends an estimation of umbilical cord bilirubin should be done in all neonates [23].

The sensitivity and specificity of UCB cut-off of 2 mg/dL was 75.2% and 60.7% as compared to the sensitivity and specificity with UCB cut-off of 2.5 mg/dL was 35.4% and 89.6%. Thus, UCB cut-off of 2 mg/dL had a better sensitivity and UCB 2.5 mg/dL had a better specificity. Haridas K et al., found that the relation between cord bilirubin level and the requirement of phototherapy is present and that the sensitivity was 58.33% and specificity was 96.49% [24].

Knupfer M et al., found that there is a high sensitivity of 97% and low specificity of 41.4% when UCB of 30 µmol/L (1.76 mg/dL) was used to predict neonatal hyperbilirubinaemia [20]. Carbonell X et al., found that if the UCB cut-off of 37 µmol/L (2.1 mg/dL) is used, it had low sensitivity of 22.2%, but high specificity of 94.7% [25]. Anand K et al., found that if the cord bilirubin ≥2.1 mg/dL, the predicted day 3 serum bilirubin is >15 mg/dL with sensitivity of 88% and PPV of 77.49% [26].

The cut-off values for UCB by ROC curve analysis in this study was 2 mg/dL which was in concordance with the studies done by Taksande A et al., and Sun G et al., [27,28]. Various other studies in this field by Sharma I et al, Knudsen A and Ahire N et al., have found cord bilirubin cut-offs as 1.9, 2.1 and 3 mg/dL, respectively [29-31].

The risk of hyperbilirubinemia when BAR cut-off of 0.59 was 36.4% (160 babies out of 439 babies who had BAR >0.59) whereas the risk of hyperbilirubinemia on taking BAR cut-off of 0.69 was 46.9% (84 babies out of 179 babies who had BAR >0.69). BARs are found to have statistically significant positive correlation with the risk of hyperbilirubinemia with a p-value of <0.001. This implies that as the BAR increases, the risk of hyperbilirubinemia also increases. The sensitivity and specificity with BAR 0.59 are 65% and 64.2%, respectively and that with 0.69 are 43.5% and 80.5%, respectively. Thus, BAR 0.59 has a better sensitivity and BAR 0.69 has a better specificity for the detection of neonatal hyperbilirubinemia. This was in close proximity to the cut-off ratio of 0.6 with a sensitivity of 83.3% and specificity of 85.7% in the study by Mashad GM et al., [16]. Cut-offs found by Sharma I et al., and Khairy MA et al., in their studies are 0.719 and 0.78, respectively [29,32]. Bhat JA et al., found that cord blood bilirubin/albumin ratio >0.98 can predict hyperbilirubinemia with sensitivity 78.79% and specificity 95.51% [15]. The different sample sizes and different methods of bilirubin estimation would have contributed to this variation in the BAR. On ROC analysis the area under UCB was 0.742 and the area under the BAR was 0.698. Sharma I et al., found the area under the ratio curve as 0.932 [29].

Strengths of the study are the large sample size of 1025 babies, unbiased enrolment and uniform technique of bilirubin estimation for all babies.

Limitation(s)

Limitations of the study are that preterm or any high-risk babies were not evaluated.

CONCLUSION(S)

This study demonstrated that both UCB and BAR are potentially useful screening tools for the detection of neonatal hyperbilirubinemia. However, it was found that UCB is a better predictor of the development of neonatal hyperbilirubinemia than BAR with UCB cut-off 2 mg/dL having a better sensitivity of 75.2% and UCB cut-off 2.5 mg/dL having a better specificity of 89.6%. Thus, UCB had a better sensitivity and specificity than the BAR in the detection of hyperbilirubinemia.

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