Original Research Article

Umbilical cord albumin and serum bilirubin as predictive factors for hyperbilirubinemia in term neonates

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ABSTRACT

Background: Hyperbilirubinemia is one of the common causes of neonatal admission. As clinical evaluation may cause a delay in identification and subsequent initiation of medical therapy, there is a need for the sensitive and inexpensive predictive marker for hyperbilirubinemia in neonates. Measurement of cord albumin and its correlation with the serum bilirubin is one of the noninvasive predictive markers for Hyperbilirubinemia. The present study carried out to know the significance of umbilical cord albumin level as a predictor of neonatal hyperbilirubinemia.
Methods: It is a hospital-based prospective cohort study, total 100 healthy term new-borns admitted in the Neonatal Intensive Care Unit, were included in the study as per study protocol over a period of one year. The blood sample was collected from umbilical cord blood for the analysis of bilirubin and albumin, and post 72 hours of life venous blood obtained for estimation of serum bilirubin and albumin along with direct and indirect Coombs test.
Results: In this study most of the patients were in the gestational age of 37-38 weeks (71%) followed by 38-40 weeks (27%) and only 1% are >40 weeks. A positive correlation was observed between cord blood bilirubin, serum bilirubin, serum albumin, and cord blood albumin levels. Cord blood albumin was a better marker for neonatal hyperbilirubinemia with a sensitivity of 83%, and a specificity of 48%; as compared to cord blood bilirubin with a sensitivity and specificity of 73% and 39% respectively.
Conclusions: From this study, cord blood albumin level was demonstrated as a good predictive marker for neonatal hyperbilirubinemia with a sensitivity of 83.1%. and specificity 48.8%. Hence, cord blood albumin may be used as a non-invasive predictor for neonatal hyperbilirubinemia.

Keywords: Albumin, Bilirubin, Cord blood, Neonatal hyperbilirubinemia

INTRODUCTION

Hyperbilirubinemia is one of the major causes of neonatal morbidity and its sequelae. In today's era of early discharge of neonate and mother following a vaginal delivery, it has become a major cause of readmission to the hospitals.[1] Idiopathic neonatal jaundice can be seen in up to as high as 60%-80% of healthy newborns.[2] Risk factors for hyperbilirubinemia include cephalohematoma or significant bruising, early gestational age, exclusive unsuccessful breastfeeding, isoimmune or other hemolytic anemia, and a sibling with a history of neonatal jaundice.[3] A lot of times, neonates can develop significant CNS complications (e.g. kernicterus) as clinical evaluation may cause a delay in identification and subsequent initiation of medical therapy.[4]

In such a scenario, it becomes necessary to have a sensitive and inexpensive predictive marker for hyperbilirubinemia in neonates.[5] Total serum bilirubin levels are usually 1-3 mg/dl at birth and peaks by 5-15 days and thereafter, declines by 3 weeks.[6]

Several previous studies have postulated the potential of cord blood bilirubin as a non-invasive and quick biochemical marker for predicting neonatal hyperbilirubinemia.[7-9] However, a recent survey by the UK National Health and Care Excellence (NICE) concluded that it was not a useful index of risk.[10]

In recent times, cord blood albumin has also been studied as a marker for the same. Albumin binds to unconjugated bilirubin and helps in its transport. This, in turn, reduces the bilirubin toxicity on the tissues by competing with tissues for bilirubin binding.[11] Low production of albumin will lower its transport and binding capacity and hence aid the determination of at-risk neonates early to avoid the complications associated with neonatal jaundice.[5]

However, there is a lack of clinical trials on the comparative accuracy of both methods (Cord blood albumin Vs Cord blood bilirubin as predictor for Hyperbilirubinemia), especially in Indian settings. Hence this study was conceived to determine the single most efficacious biochemical test for predicting neonatal hyperbilirubinemia and preventing its sequelae.

METHODS

It was a hospital-based prospective cohort study carried in for total 100 healthy term newborns admitted in the Neonatal Intensive Care Unit (NICU), Department of Pediatrics Teerthankar Mahaveer Medical College and Research Center (TMMC and RC) Moradabad (U.P.), over a period of one year from June 2018- June 2019.

Inclusion criteria

- All healthy term neonates sequentially born in the hospital with consenting mothers were taken up for the study

Exclusion criteria

- Neonates born with gross congenital anomaly/ other medical/surgical illnesses
- Neonates born with jaundice/ having jaundice on day 1 of life
- Neonates who left the hospital against medical advice
- All non-consenting parents were excluded from the study.

Sample collection

Blood samples, obtained from umbilical cord vein, from neonates were collected in plain vials. Assays were done within 2 hrs of sample collection and invariably within 24 hrs for estimation of cord blood bilirubin and albumin. Neonatal blood group was also determined from the samples. All the patients were regularly followed up with a clinical examination for development of subsequent

neonatal jaundice. Post >72 hrs of life, venous samples were obtained from all the neonates under all aseptic precautions and sent to the lab on the same day for estimation of serum bilirubin and albumin along with Direct and indirect Coombs test.

Laboratory estimation of serum bilirubin and albumin

For estimation of cord blood and serum albumin, Bromo cresol green (albumin reagent) was used. Albumin binds with Bromo Cresol Green (BCG) at pH 4.2 causing a shift in the absorbance of the yellow BCG dye. The blue green colour formed is proportional to the concentration of albumin, when measured photometrically b/w 580-630 nm with maximum absorbance at 625 nm, active ingredients include Bromo creosol green, succinate buffer, and sodium azide, a surfactant.

For estimation of cord and serum bilirubin, bilirubin direct reagent will be used, for quantitative determination in vitro. The azobilirubin produced by the reaction between bilirubin and the diazonium salt of sulfanilic acid shows maximum absorption at 550 nm in the acid medium.

Data analysis

The collected data was compiled using MS Excel 2007 and statistical analysis was done using SPSS software 21.0. Various tests of significance were applied, and ROC curve was plotted. A p value of less than 0.05 was taken as significant to establish correlation among different variables.

RESULTS

The data analysis revealed that most of the patients were in the gestational age of 37-38 weeks (71%) followed by 38-40 weeks (27%) and only 1%, >40 weeks, making the mean gestational age as 37.9 weeks. 69% of patients had a birth order of 1 or 2, and 31% had birth order of 3 and above. Most common baby blood group was B+(47%), followed by A+ and O+ in the order of 19% and 17% respectively. 66% of the study subjects were delivered by caesarean section, while 34% were delivered vaginally (Table 1).

The mean value of birth weight, cord blood albumin, cord blood bilirubin, serum albumin, and serum bilirubin (total) of the study are 2.6 kg, 3.2 g/dl, 2.3 mg/dl, 11.2 mg/ dl respectively (Table 2).

Among the babies who developed clinical jaundice, only 18% required phototherapy, while 2% had to be admitted under neonatal intensive care unit.

The development of significant hyperbilirubinemia was not statistically associated with gender of the baby, mode of delivery, birth weight, gestational age, birth order of the baby or maternal blood group.

In this study author found a moderate positive Co-relation between the cord blood bilirubin (total) and serum bilirubin(total) with 'r' value 0.38 (Table 3). While there is strong positive Co-relation between the cord blood albumin and serum albumin with 'r' value 0.94 (Table 4 and Figure 1).
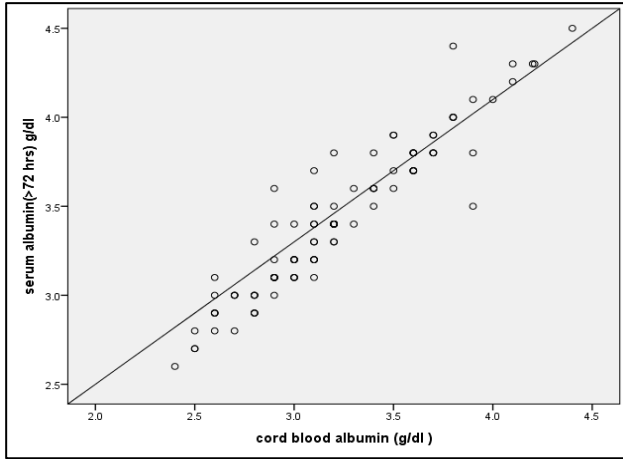

Figure 1: Co-relation between the cord blood albumin and serum albumin among newborn babies.

In this study authors found a weak positive co-relationship between cord blood bilirubin (Direct) and serum bilirubin (Direct) with 'r' value of 0.27. While there is moderate positive co-relationship between cord blood bilirubin (Indirect) and serum bilirubin(Indirect) with 'r' value of 0.39.

Table 1: Frequency and percentage distribution of sample characteristics (maternal characteristics and newborn characteristics) (n=100).

Sample Characteristics		n	%
Maternal blood group	O+	39	39.0
	A+	21	21.0
	B+	23	23.0
	AB+	11	11.0
	0-	2	2.0
	B-	4	4.0
Mode of delivery	NVD	34	34.0
	LSCS	66	66.0
Period of gestation (Ballard's Weeks)	36-38	71	71.0
	38-40	27	27.0
	40-42	1	1.0
Gender of baby	Male	44	44.0
	Female	56	56.0
Birth order	1	31	31.0
	2	38	38.0
	3	15	15.0
	4	9	9.0
	5	5	5.0
	6	1	1.0
	7	1	1.0
Baby blood group	O+	17	17.0
	A+	19	19.0
	B+	47	47.0
	AB+	17	17.0

Table 2: Mean and standard deviation of maternal and newborn characteristics (N=100).

No	Maternal and new born characteristics	Mean	Standard Deviation	Minimum	Maximum
1	Gestational Age	37.9	0.91	36.4	40.4
2	Birth Weight	2.6	0.50	1.60	4.50
3	Length of Baby	47.3	2.7	41.0	52.0
4	Head Circumference	35.1	1.4	30.3	38.6
5	Cord bloodalbumin (g/dl)	3.2	0.44	2.4	4.4
6	Serum albumin (mg/dl)	3.4	0.42	2.6	4.5
7	Cord blood bilirubini (Total) mg/dl	2.3	1.06	0.5	9.1
8	Serum blood bilirubini (Total) mg/dl	11.2	2.97	4.2	18.9

Table 3: Co-relation between the cord blood bilirubin (Total) and serum blood bilirubin (Total) among newborn babies.

	Mean	Standard deviation	Correlation coefficient (r)	p value
Cord blood bilirubin (Total) mg/dl	2.341	1.0622	0.38	0.001*
Serum blood bilirubin (Total) mg/dl	11.233	2.9768		

Table 4: Co-relation between the cord blood albumin and serum albumin among newborn babies.

Variable	Respondents	Correlation and coefficient(r) value		p value
	Mean	Standard deviation		
Cord blood albumin(g/dl)	3.214	0.44	0.94	0.001*
Serum albumin(mg/dl)	3.427	0.42		

Table 5: Co-relation between the cord blood albumin and serum blood bilirubin (> 72hrs) among newborn babies.

Variable	Respondents		Correlation and coefficient (r) value	p value
	Mean	Standard deviation		
Cord blood albumin(g/dl)	3.214	0.44	-0.36	0.001*
Serum bilirubin i(Total)mg/dl	11.2	2.97		

Table 6: Relationship between level of cord albumin and development of hyperbilirubinemia.

		Cord Blood Albumin groups				
		< 3.2 g/dl		3.2 and above 3.2 g/dl		
		Count	%	Count	%	Total
Hyperbilirubinemia	Positive	29	58	12	24	41i (41%)
	Negative	21	42	38	76	59i (59%)
	Total	50	100	50	100	100i (100%)

Table 7: The sensitivity and specificity of cord blood albumin in determining significant hyperbilirubinemia.

Area under curve	p value	95% of Confidence Interval		Cutoff value	Sensitivity (%)	Specificity (%)
0.724	0.001	0.620	0.827	2.95	83.1	48.8

Table 8: The sensitivity and specificity of cord blood bilirubin in determining significant hyperbilirubinemia

Area under curve	p value	95% of Confidence Interval		Cutoff value	Sensitivity (%)	Specificity (%)
0.760	0.001	0.666	0.854	2.15	73.2	39.0

Table 9: Comparative analysis of sensitivity and specificity of predictive markers of hyperbilirubinemia.

Diagnostic Modality	Area under curve	Sensitivity (%)	Specificity (%)
Cord blood Bilirubin	0.760	73.2	39.0
Cord blood Albumin	0.724	83.1	48.8

Figure 2: ROC Curve showing cord blood albumin sensitivity and specificity in detecting significant hyperbilirubinemia.
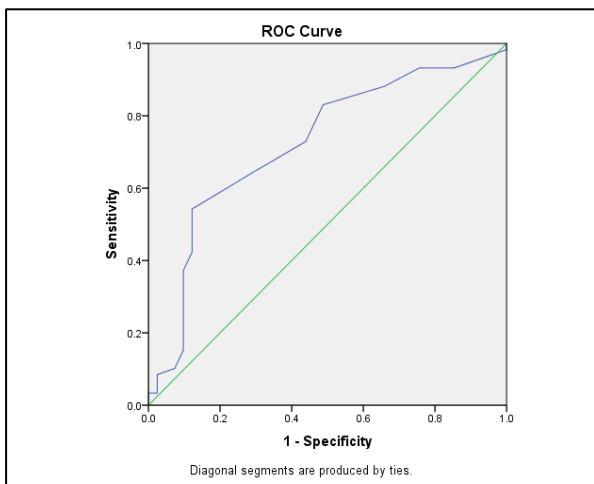

Figure 3: ROC Curve showing cord blood bilirubin sensitivity and specificity in detecting significant hyperbilirubinemia.

A significant (p value=0.001) negative co-relationship was observed between cord blood albumin and serum total bilirubin(>72 hrs) with 'r' value -0.36 (Table 5).
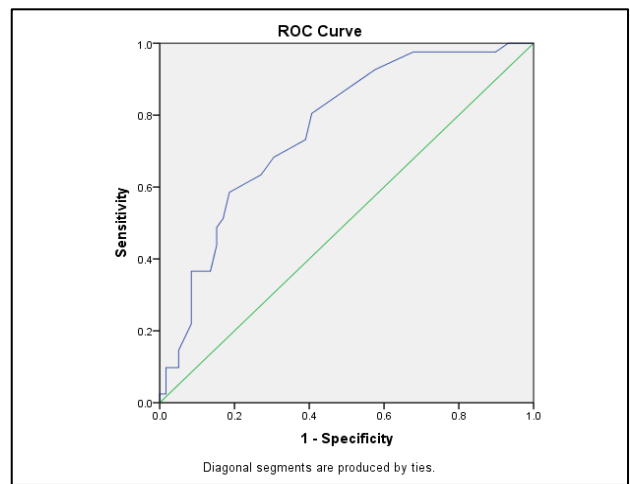
At < 3.2 g/dl and ≥3.2 g/dl cord blood albumin, 29 (58%) and 12(34%) newborns developed hyperbilirubinemia respectively (Table 6).ROC curve shows that area under

curve was 0.724 of total area (Figure 2) with p value 0.001(<0.05) indicating the usefulness of the test in predicting Hyperbilirubinemia. A cutoff level of cord blood albumin of 2.95 g/dl as obtained by ROC curve was determined to have sensitivity and specificity of 88.1%, 48.8% respectively in the prediction of significant hyperbilirubinemia (Table 7).

ROC curve shows that area under curve was 0.760 of total area, p=0.001 indicating the usefulness of the test in predicting Hyperbilirubinemia (Figure 3).

A cut-off level of cord blood bilirubin of 2.15mg/dl as obtained by ROC curve was determined to have 73.2% of sensitivity and specificity 39.0% in the prediction of significant hyperbilirubinemia (Table 8).

DISCUSSION

An in-depth analysis of results revealed a uniform sex ratio with no significant correlation with the development of hyperbilirubinemia in 72 hours. However, studies done by Satrya and Maisels and Kring had shown that male babies are at a higher risk of developing icterus and subsequent intervention for icterus.[12-13] But the present study is in correlation with the study done by Taksande et al, which states that there is no relation between neonatal hyperbilirubinemia and the sex of the baby.[14] Most of the babies were in the gestational age of 37-38 weeks (71%). Babies with birth order of 2 formed the major arm of the study population. B+ was found to be the most common blood group, which was in concordance with the national data. Out of the study population of 100 babies, 41% developed hyperbilirubinemia, out of which 18% underwent phototherapy and 2% had to be admitted under the neonatal intensive care unit. In the current study, it was noted that there was no relation between the mode of delivery and the development of icterus and the cord albumin levels were not significantly different. This was in correlation with the studies done by Sun G et al, and opposed to a study by Knusden et al, who claimed no significant correlation.[8,15]

The study also threw light on a positive correlation between cord blood albumin and serum albumin levels, with a significant p-value of <0.05; this was in concordance with a study by Awasthi et al., who stated similar results.[16] The present study also showed a moderate positive correlation between cord blood bilirubin and subsequent hyperbilirubinemia, with moderate positive correlation with indirect bilirubin levels in serum on Day 3 of life. It was in accordance with a similar Indian study by Pahuja et al, who also demonstrated positive results.[17]

The present study also calculated the sensitivity and specificity of the cord blood albumin and bilirubin levels as markers for predicting hyperbilirubinemia. The comparative analysis is as follows (Table 9).

From this study, cord blood albumin level was demonstrated as a good predictive marker for neonatal hyperbilirubinemia with a sensitivity of 83.1%. It was higher than a recent study by Pahuja et al, who found a sensitivity of only 63.1%;18 and another study from the Indian subcontinent by Nahar et al, who found a sensitivity of 98.6%.[18] However, the specificity of cord blood albumin as a predictive marker was less compared to these studies.

The present study also shows that cord blood albumin level is a better predictor for the development of neonatal hyperbilirubinemia, with better sensitivity and specificity as compared to cord blood bilirubin levels. The results were also strikingly similar to an Indian study by Aiyappa et al, who observed similar results, and concluded that cord blood albumin levels of less than 2.8 gm/dl are associated with risk of development of clinical icterus.[19]

CONCLUSION

Through this study, authors promote the use of serum albumin in conjunction with serum bilirubin as a predictive marker for neonatal hyperbilirubinemia. This should be done especially in cases that are at high risk of development of clinical jaundice.

The cost-effectiveness of this simple diagnostic modality also makes it a useful tool in low resource settings. Hence, promotion to further research should be given in this field, and more research should be done to validate its use on an extensive scale.

ACKNOWLEDGEMENTS

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