Original Research Article

Prediction of neonatal hyperbilirubinemia by cord blood analysis to diagnose subsequent hyperbilirubinemia

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ABSTRACT

Background: the study was aimed to determine the predictive value of cord bilirubin and 24th hour serum bilirubin levels in identifying newborn babies at risk of developing significant hyperbilirubinemia.

Methods: A total 300 term neonates with a mean birth weight of 2.58±0.23 kg ranging from 1.92 kg-4.1kg were included in this study. Under strict aseptic precautions cord blood sample were collected from all newborns for analysis of serum bilirubin levels, and haemoglobin levels.

Results: The incidence of significant hyperbilirubinemia in this study was 14%. Among jaundiced newborns sex ratio M/F:1.6:1(male female ratio 1.1:1). Mean Cord bilirubin levels in babies who subsequently developed hyperbilirubinemia was 2.798±0.5559 mg/dl and in others were 1.511±0.3260 mg/dl and the difference was statistically significant. There was a statistically significant correlation between cord bilirubin and neonatal jaundice. Cord bilirubin ≥2 mg/dl had good predictive value in identifying newborns who are likely to develop significant hyperbilirubinemia later.

Conclusions: Babies with cord blood bilirubin ≥2 mg/dl can be followed up in the hospital for 5 days, the time of peak neonatal hyperbilirubinemia to prevent the babies discharged early and later readmission for neonatal hyperbilirubinemia.

Keywords: Cord blood, Cord blood bilirubin, Hyperbilirubinemia

INTRODUCTION

Neonatal hyperbilirubinemia is a major concern for both parents and pediatricians. Jaundice is a cause of concern not only due to its staining character but also because of potential brain damage caused by it. It is one of the preventable cause of deafness and mental retardation. Though in most cases a benign problem nevertheless untreated, severe unconjugated hyperbilirubinemia is potentially neurotoxic and conjugated hyperbilirubinemia is a harbinger of underlying serious illness.[1]

Neonatal Jaundice is evidenced in two thirds of entirely healthy term newborns and in a greater proportion of preterms (80%) in the first week of life[1]. This is a reflection of liver's immature excretory pathway for bilirubin at a time of heightened production.

The resultant jaundice is referred to as physiological jaundice. However non physiological or pathological hyperbilirubinemia is known to occur in 5-10 % of healthy term newborns and is the most common reason for readmission during early newborn period.[1-5]

As there is no cut off value of bilirubin level that can cause bilirubin encephalopathy, neonatal jaundice has become a serious cause of concern for both parents and paediatricians as well.[6] Thus every jaundiced baby

necessitates attention at the earliest to look for the features of pathological jaundice.

After the reports of kernicterus occurring in healthy newborns even without haemolysis, have come to the fore front, there has been an increased apprehension with regard to jaundice. In the current era of early postnatal discharge of mothers and babies from the hospital, (as it is not possible to keep the mothers and babies for a long time in the maternity ward) it is vital to identify the newborns at risk of significant hyperbilirubinemia before they are discharged from the hospital and intervene.

The American Academy of Pediatrics (AAP) recommends that neonates discharged within 48 hours of life should have a follow-up visit after 2-3 days to detect significant jaundice.[7] But however this not possible in our country due to limited follow up facilities in the locality. Hence the concept of early prediction has become crucial to spot the newborns at risk of significant jaundice. Therefore, prediction of significant hyperbilirubinemia using cord bilirubin and first day serum bilirubin has been attempted, in order to implement early treatment and there by minimize the risk of bilirubin dependent brain damage.

The current study designed to determine the predictive value of cord bilirubin and 24th hour serum bilirubin levels in identifying newborn babies at risk of developing significant hyperbilirubinemia and to identify the correlation between the cord bilirubin, 24th hour serum bilirubin and the clinical risk factors.

METHODS

The present study conducted on 300 term newborns in the Department of Pediatrics, Narayana Medical College and Hospital, Nellore, Andhra Pradesh, a tertiary care center. The study conducted between December 2016 to September 2018 with a predesigned proforma aided the enrolment of the newborns into the study.

Gestational age of each baby was assessed with the aid of LMP, EDD and antenatal ultrasound dating and it was confirmed by using New Ballard's score .For feasibility only those babies, whose families were residents of Nellore, who could be followed up till the end of the study on day 5 were taken into the study.

Inclusion criteria

Healthy term newborn babies delivered in Narayana Medical College and Hospital, Nellore.

Exclusion criteria

- Extremely low birth weight babies
- Preterm newborns
- Neonates with major congenital malformations
- Sick neonates or babies admitted to NICU.

Procedure

Approval from the Institutional Ethical Committee of Narayana Medical College and Hospital, Nellore was obtained. 300 Newborns delivered in NMC who satisfy the inclusion criteria were included in the study. Under strict aseptic precautions cord blood sample were collected from all newborns for analysis of serum bilirubin levels, and haemoglobin levels. This method is based on the fact that diazonium salt 3,5-dichlorophenyl diazoniumtetrafluoroborate (DPD) couples directly with direct (conjugated) bilirubin into produce direct azobilirubin. The absorbance of this dye is directly proportional to the direct bilirubin in the sample. Complete blood picture, peripheral blood smear, septic screen, reticulocyte count, direct coombs test (DCT), blood grouping and Rh typing of mother and baby hematocrit, were done whenever necessary.

The values of day 5 bilirubin were compared with cord blood bilirubin levels. The main outcome of the study was inferred in terms of hyperbilirubinemia. Serum bilirubin level ≥15 mg/dl in first 5 days of life was taken as significant hyperbilirubinemia. Babies with icterus upto the palms and soles and with significant hyperbilirubunemia (total serum bilirubin levels >15 mg/dl) were kept under phototherapy as per the unit guidelines. Babies with significant jaundice on day 5 were investigated further.

Statistics

Data was analysed using a computer aided statistical package SPSS. The statistical methods used were ANOVA, Chi-Square test, Odds ratio, multiple logistic forward stepwise, multiple logistic regression likelihood ratio, student's test and ROC curves. The critical cord bilirubin level having the highest sensitivity and specificity was determined with the Receiver operating characteristics (ROC) curve analysis. ROC curves were plotted using 1-specificity on the x axis and the sensitivity on the y axis. Cord serum bilirubin levels were used for developing 'prediction test'. The sensitivity and specificity were for predicting hyperbilirubinemia.

RESULTS

300 cases of term newborn babies were studied during the period from December 2016 –May 2018 with reference to neonatal hyperbilirubinrmia etiology and correlation between the cord bilirubin, 24 hour serum bilirubin and clinical risk factors. The following results were made from the study. Sex ratio was M:F=158:142= 1.1:1. This study showed nearly equal distribution of male and female babies.

Distribution of babies according to mode of delivery

This study included neonates born by Vaginal Delivery (VD) and caesarian (LSCS). Out of 300 babies 160

babies (53.33%) delivered by vaginal delivery and 140 babies delivered by caesarean delivery.
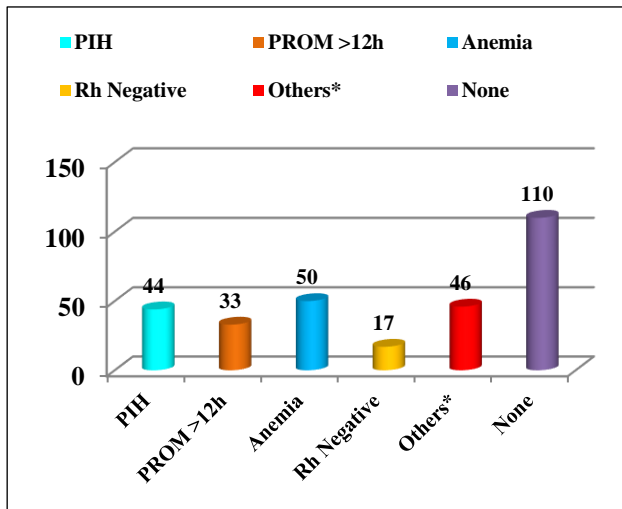
In majority of cases mode of delivery was Vaginal Delivery (includes both spontaneous and assisted vaginal deliveries).

Parity wise distribution of babies

In the present study out of 300 babies 121 babies (40.33%) born to primi mothers and 179 babies (59.66%) born to multipara mothers. In this study more number of babies born to multi gravid were present.

Distribution of babies according to antenatal complication

There was an overlap of antenatal complications in some cases. 36.6% of cases had no antenatal complications. Anemia was seen in 16.66% and PIH was seen in 14.6% of cases (Figure 1).

Others* include oligo /polyhydramnios, bad obstetric history, IDM, peripartum fever, APH, Chronic Systemic disease.

Figure 1: Distribution according to antenatal complications.

In the present study oxytocin induced labor was seen in 40% of cases (Table 1).

Table 1: Distribution according to intrapartum drug administration.

Drugs	N	%
Oxytocin	119	39.66%
local / Spinal/ General anesthetics	140	46.66%
None	41	13.66%
Total	300	100%

Mean birth weight of all the babies was 2.604±0.42 kg ranging from 1.9 kg to 4.1 kg. Mean cord blood bilirubin was 1.691±0.577 mg/dl (Table 2).

Out of 300 babies, 42 (14%) developed significant jaundice by day 5. Mean birth weight of these babies with jaundice was 2.681±0.427 kg, ranging from 1.9 to 4.1 kg. (Table 3).

Table 2: Group statistics showing demographic parameters of all the babies.

Parameter	N	Mean	Std Deviation	Range (min-max)
Birth wt (kg)	300	2.604	0.428	1.9-4.1
Cord blood TSB (mg/dl)	300	1.691	0.577	1.0-3.6

Table 3: Demographic parameters of jaundiced babies.

Parameter	N	Mean	Std deviation	Range
Birth wt (kg)	42	2.681	0.427	1.9-4.1
Cord blood TSB (mg/dl)	42	2.798	0.555	1.1-3.6

Association between the hyperbilirubinemia and sex of the newborn

In the babies who developed jaundice 26 (61.9%) were males and 16 (39.09%) were females. M:F sex ratio was 1.62:1. In the present study there is no significant difference (P value 0.196) in the incidence of hyperbilirubinemia among both sexes.

Hence, the present study infers that the serum bilirubin level is independent of the sex of the newborn.

Association between the mode of delivery and the neonatal hyperbilirubinemia

Babies born by vaginal delivery had higher incidence of neonatal jaundice. In the present study there is no significant association (p=0.229) between the neonatal hyperbilirubinemia (≥15 mg/dl) and the mode of delivery. This implies that neonatal hyperbilirubinemia is independent of the mode of delivery.

Association between the parity of mother and neonatal hyperbilirubinemia

Babies born to multi gravida had higher incidence of Jaundice (54.76%) (n=23). 19 babies (45.23%%) born to Primigravida had Jaundice. In this study, there was no significant association between the neonatal hyperbilirubinemia and parity of mother.

In this study there is no association between the neonatal hyperbilirubinemia and PIH, PROM and maternal anemia. There is significant association between the Rh negative pregnancy and neonatal hyperbilirubinemia (Table 4).

Table 4: Association between the hyperbilirubinemia and antenatal complications.

ANC	Jaundiced	No jaundice	Total	P value
PIH	6	38	44	0.940
Prom >12 hrs	4	29	33	0.742
Anemia	3	47	50	0.074
Rh Neg	8	9	17	0.0001

There is no association between the neonatal hyperbilirubinemia and oxytocin induction of labour (Table 5).

Table 5: Association between the neonatal hyperbilirubinemia and oxytocin induction of labour.

Drugs	Jaundiced	Non jaundice	Total	P value
With oxytocin	16	103	119	
Without oxytocin	26	155	181	0.822
Total	42	258	300	

Cord bilirubin level of ≥ 2 mg/dl cut off value is chosen based on the Receiver operating characteristic (ROC) analysis. ROC curve for cord bilirubin in graph 14, show

that, the area under curve was 0.946 of total area, p <0.0001 indicating the usefulness of cord bilirubin in predicting the neonatal hyperbilirubinemia (Table 6).

Table 6: Association between the neonatal hyperbilirubinemia and the critical cord bilirubin levels (≥ 2 mg/dl).

Neonatal hyperbilirubinemia	Cord bilirubin		Total	P value
	≥ 2 mg/dl	<2 mg/dl		
Present	38	4	42	
Absent	39	219	258	0.0001
Total	77	223	300	

In the present study, cord blood bilirubin level of ≥ 2 mg/dl having the sensitivity of 90.48%, specificity 84.88%, positive predictive value 49.35% and the negative predictive value 98.21% in prediction of neonatal hyperbilirubinemia (p value <0.0001).So the cord blood bilirubin of ≥ 2 mg/dl can be used as an early predictor of neonatal hyperbilirubinemia.

In the present study there is no significant association between the sex of the neonate, mode of delivery, gravida of mother, intrapartum oxytocin administration, PIH, PROM and maternal anemia with neonatal hyperbilirubinemia (Table 7).

Table 7: Comparison of Demographic Parameters in Babies with and without jaundice.

Variables		Jaundice (n=42)	Non jaundice (n=258)	P value
Sex	Male	26	132	0.196
	Female	16	126	
Mode of delivery	Vaginal	26	134	0.230
	Caesarean	16	124	
Gravida	Primi	19	102	0.485
	Multi	23	156	
Antenatal compilations	PIH	6	38	0.940
	PROM	4	29	0.742
	Anemia	3	47	0.07
	Rh neg	8	9	0.0001
Intrapartum oxytocin		16	26	0.822
Cephalhaematoma		11	2	0.0001
Mean birth weight		2.681±0.4278 kg	2.591±0.4275 kg	0.207
Mean cord bilirubin		2.718±0.5559 mg/dl	1.511±0.3260 mg/dl	<0.0001

DISCUSSION

There is a concern about increasing incidence of kernicterus in healthy term neonates, and hyperbilirubinemia is the most commonly reported cause for readmission during the early neonatal period. The need for early prediction of hyperbilirubinemia in the

early discharged newborns from the hospital is therefore important.

Knowledge of the infants at risk for developing jaundice allows simple bilirubin reducing methods to be implemented before bilirubin reaches critical level. This study is designed to determine the predictive value of

cord bilirubin and 24th hour serum bilirubin to identify the newborns at risk of significant hyperbilirubinemia.

Incidence of jaundice

In the present study it is found that the incidence of significant hyperbilirubinemia to be around 14% (42 out of 300). The incidence of neonatal hyperbilirubinemia varies from 5.9% to 12.8% in several previous Indian studies.

Sex of the newborn

In the present study, study group is uniformly distributed with 158 male and 142 female babies. There is no significant correlation (p value 0.916) between the neonatal hyperbilirubinemia and the sex of the newborn. Hence the present study infers that the neonatal hyperbilirubinemia is independent of the sex of the newborn. The present study is in correlation with the study done by Amar Taksande et al, Rostami et al, and Pradhan et al, (Table 8).[8-10]

Table 8: Comparison studies on the mode of delivery and neonatal hyperbilirubinemia.

Studies	Total cases	Vaginal delivery	Caesarean delivery	P value
Present study	300	160	140	O.230
Pradhan A et al[10]	202	104	98	NS
Knudsen[11]	291	-	-	NS
Amar Taksande et al[12]	200	114	66	0.527
Rudy Satrya et al[13]	88	66	22	0.885

Mode of delivery

In the present study association between the neonatal hyperbilirubinemia and the mode of delivery was studied. Out of 160 cases with vaginal delivery 26 developed serum bilirubin ≥15 mg/dl and off 140 cases with vaginal delivery 16 developed significant hyperbilirubinemia(≥15 mg/dl), with p value of 0.230. In the present study, there is no significant association between the neonatal hyperbilirubinemia and mode of delivery.

Association between the neonatal hyperbilirubinemia (≥15 mg/dl) and Oxytocin induction of labour

In the present study, there is no significant association (p value-0.822) between the neonatal hyperbilirubinemia and the oxytocin induction of labour. Out of 119 cases delivered by oxytocin induction of labour 16 developed hyperbilirubinemia and out of 181 cases who did not received oxytocin 26 babies developed hyperbilirubinemia. The present study is in correlation with the previous studies. The present study is in correlation with studies Knudsen et al, and Amar Taksande et al.[11,12] The present study is in contradiction to the studies by Rostamiet al, which showed significant association between the neonatal hyperbilirubinemia and oxytocin induction of labour.[9]

Association between the neonatal hyperbilirubinemia and antenatal complications

In the present study there is no significant association between the neonatal hyperbilirubinemia and the pregnancy induced hypertension with P value 0.940. Other studies are Awasthi et al, with p value of 0.5 and Amar Taksande et al, with P value 0.06 showed no association between the neonatal hyperbilirubinemia and pregnancy induced hypertension.[14,12]

Table 9. Comparison studies on the predictive ability of cord blood bilirubin levels and neonatal hyperbilirubinemia.

Studies	No. of babies	Cut off cord TSB (mg/dl)	Cut off neonatal hyperbilirubinemia	Sensitivity	Specificity	PPV	NPV
Present study	300	≥2	≥15	90.48%	84.88%	49.35%	98.21%
Zakia Nahar et al[15]	84	≥2.5	≥17	77%	98.6%	91%	96%
Pradhan A et al[10]	202	>2.5	>15	84.1%	88.5%	98%	45.1%
Sehgal et al[16]	100	>2.02	>14	87.5%	70.8%	39%	96.5%

So, the present study is in correlation with the other studies. In the present study there is no association between the neonatal hyperbilirubinemia and PROM (P value: 0.742). In the present study there is no association between the neonatal hyperbilirubinemia and maternal anemia (P value: 0.074) In the present study, on ROC

curve analysis critical cord bilirubin level (≥2 mg/dl) with high sensitivity and specificity was selected. Critical cord bilirubin level ≥2 mg/dl has sensitivity of 90.48%, specificity of 84.88%, PPV of 49.35% and NPV of 98.21% in predicting the risk of developing significant hyperbilirubinemia. Several studies are published on the

usefulness of cord bilirubin level in prediction of hyperbilirubinemia.

Nahar Z et al, in 2009 showed that cord bilirubin >2.5 mg/dl has sensitivity 77%, specificity 98.6%, with PPV of 91% and NPV of 96% in predicting the neonatal hyperbilirubinemia.15 This study is in correlation with the present study (Table 9).

Pradhan A et al, showed that cord bilirubin level >2.5 mg/dl has sensitivity of 84.1%, specificity of 88.5%, PPV of 98% and NPV of 45.1% for predicting the risk of developing pathological jaundice, is in correlation with present study.10 Pahuja M et al, also are in correlation with present study.[17]

The present study infers that the critical cord bilirubin level ≥2 mg/dl can be used as early predictor of neonatal hyperbilirubinemia.

CONCLUSION

Cord bilirubin ≥2 mg/dl had found to have good predictive value in identifying newborns who are likely to develop significant hyperbilirubinemia later. With the above criteria, newborns who are at low risk to develop hyperbilirubinemia can be identified and discharged early. Babies with cord blood bilirubin ≥2 mg/dl can be followed up in the hospital for 5 days, the time of peak neonatal hyperbilirubinemia to prevent the babies discharged early and later readmission for neonatal hyperbilirubinemia.

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