ORIGINAL RESEARCH PAPER

Paediatrics

"EARLY BILIRUBIN ESTIMATION IN PREDICTING NEONATAL HYPERBILIRUBINEMIA IN NEWBORN BABY MORE THAN 35 WEEKS OF GESTATION"

KEY WORDS: Cord Bilirubin , Phototherapy, Early Discharge, Less Readmissions

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ABSTRACT

Aims And Objective : a) To assess whether umbilical cord bilirubin (UCB) level at delivery predicts the development of neonatal jaundice in newborn more than 35 weeks. b) To estimate the development of targeted primary therapy and follow up for early estimation of infants at high risk. **Methodology :** Cord billirubin of neonates >35 weeks of gestational age were taken at birth and compared with serum bilirubin (total and direct) at 24 hrs and with neonatal jaundice at 3-5 days as per NICE (National Institute for Health and Clinical Excellence) guidelines. 2ml of cord bilirubin taken in a plain vial at birth . Neonates with ABO or Rh incompatibility or hemolysis due to any other cause are taken into account. **Study Design:** Hospital based prospective observational study at Hi-Tech Medical College andHospital from September 2020 to October 2022 on neonates born with gestation of >35 weeks . **Result** : 102 neonates >35 weeks were taken .ROC analysis for evaluating the cord bilirubin total of serum as a marker of neonatal jaundice. Total cord bilirubin values at three time periods have been taken- after birth, 24 hours and 72 hours of birth have been observed. Area under the ROC curve was 0.797 (CI: 0.694 to 0.900), 0.768 (CI: 0.667 to 0.863) and 0.953 (CI: 0.913 to 0.992) for cord bilirubin total at birth, 24 hrs 72 hrs of birth respectively. The AUC for cord bilirubin was found to be significant for all the three time points ($p<0.001$). The cut off value for cord bilirubin at birth as a marker of neonatal jaundice was >1.64 with sensitivity 90.28, 95% CI (81.0-96.0), specificity 60, 95% CI (40.6-77.3), positive likely hood ratio 2.26, 95% CI (1.45-3.52) and negative likely hood ratio 0.16, 95% CI (0.076-0.35). The cut off value for cord bilirubin at 24 hours of birth as a marker of neonatal jaundice was >5.81with sensitivity >5.81, specificity 66.67, 95% CI (47.2-82.7), positive likely hood ratio 2.42, 95% CI (1.44-4.06) and negative likely hood ratio 0.16, 95% CI (0.076-0.35). The cut off value for cord bilirubin at 72 hours of birth as a marker of neonatal jaundice was >14.3with sensitivity 86.11, 95% CI (75.9-93.1), specificity 96.67, 95% CI (82.8-99.9), positive likely hood ratio 25.83, 95% CI (3.75-177.85) and negative likely hood ratio 0.14, 95% CI (0.081-0.26). **Conclusion**: Cord bilirubin could be useful to determine newborns at a risk of developing hyperbilirubinemia and prevent developing severe complications due to delay in diagnosis.

INTRODUCTION

Hyperbilirubinemia is a common and, in most cases, benign problem in the neonatal period that is often physiologic, and interventions are not usually necessary.[1]

Neonatal hyperbilirubinemia is a clinical condition this is common in paediatric practice and constitutes one of the major issues within the neonatal period accounting for prolonged hospital stay.If the concentration of serum bilirubin in adults was higher than 2 mg/dL, there would be yellowish pigmentation of skin and sclera; in case the newborns had a wealth of capillaries, when the concentration of serum bilirubin was higher than 5 mg/dL, their skin would show visible yellow [2].Over 50% of all newborn infants become visibly jaundiced.[3]

On the other hand, neonatal jaundice is an important clinical feature as it may be a sign of an underlying disorder (i.e. hemolytic anemia, infection, an inborn error of metabolism or liver disease).[4] In severe cases, high unconjugated hyperbilirubinemia can be deposited in the brain, particularly in the basal ganglia, causing kernicterus[6]

Incidence of significant hyperbilirubinemia is 10.5% in term newborns and 25.3% in near term newborns.[8]

Early discharge of heathy babies above 35 week after delivery has become a common practice because of medico-social reasons and eonomic constraints and discharged babies need to be followed up for development of hyperbilirubinemia .

Some researches (Li, 2015) showed that if umbilical cord blood was extracted immediately after delivery to determine the concentration of bilirubin, accompanied with daily continuous determination of transcutaneous jaundice, the incidence of neonatal hyperbilirubinemia can be effectively predicted in advance.[5]

A complete follow up is not always possible due to socioeconomic reasons and patient's non-compliance. Early discharge before 72 hrs had significantly increased the risk of readmission with hyperbilirubinemia.[9,10]. Identification of biomarkers that could be measured within a few hours, which robustly predict incident jaundice , would represent a significant advance.Early discharge of the healthy-term newborns after delivery has become a common practice because of both medical and social reasons as well as economic constraints.[7]

Bernaldo AJ et al. [11] concluded that in full term neonates, values of cord blood unconjugated bilirubin was significantly higher in newborns who required phototherapy.

Estimation of umbilical cord bilirubin (UCB) at delivery is practical , cheap and non-invasive . Uncontrolled jaundice often leads to bilirubin toxicity that is irreversible leading to severe neurological insult , chronic bilirubin encephalopathy,

developmental and motor delays, sensorineural deafness and mental retardation .In this study we are performing a prospective analysis to assess the potential utility of umbilical cord bilirubin in predicting clinically significant hyperbilrubinemia in neonates more than 35 weeks as per NICE guidelines.

Association Of Different Factors With Neonatal Hyperbilirubinemia

Mode Of Delivery

Statistically significant positive relationship between hyperbilirubinemia and instrumental delivery was established by some[18], though no significant association was found by others[19].

According to a recent study[20], significant hyperbilirubinemia was strongly associated with delivery by vacuum extractor while cesarean section was shown to decrease the risk.

Another multicentric study[21] done recently has shown no significant association between mode of delivery and NNHB.

Maternal Age

Some workers [22]have shown older maternal age to be statistically significantly associated with NNHB. On the other hand higher serum bilirubin levels were found in babies of younger age group mothers, by some workers.[23]

Maternal Blood Group And Nnh

Association between NNHB and blood group incompatibility was higher in same studies[23,24]and comparatively lower in others. []

With decrease in the incidence of Rh hemolytic disease, ABO incompatibility has became an important cause of jaundices in newborn babies. Direct coomb's test is usually negative in ABO incompatibility whereas in Rh hemolytic disease it is usually positive.

Two studies[24,25] ,reported 27.2% and 47% of cases of NNH was due to ABO incompatibility respectively.There was also increased percentage of O-A mother-child combination causing NNHB, whereas percentage of O-B mother child combination causing NNH was more or less same in those two studies. In one of these studies percentage of Rh negative individuals were 5% whereas according to other study Rh incompatibility causing NNH was 3.7%

Maternal Disease

Though different antenatal events like bleeding in 1st and 3rd trimester, cervical incompetence and premature rupture of membrane have statistically significant association with NNHB[29], no significant association of maternal toxaemia with development of NNH was reported by some workers.[21,18,19]

According to one study[19] maternal diabetes was associated with development of NNHB.

Type Of Feeding

Breast feeding has been reported to be associated with NNH in several studies in the past.[26-30]

Exclusive breast feeding has a different pattern of physiological jaundice as compared to artificially fed babies[31,32]. Peak bilirubin level have been 11.4 mg% in bottle fed babies as compared to 14.5 mg% in breast fed babies. Recent data suggests that the 95th centile bilirubin level is 17.5 mg% and this has been attributed to increased incidence of breast feeding.[]

Maisels and Gifford et al [10]reported that 82.7% of the infants with no identifiable cause for hyperbilirubinemia were breast fed. In a recent study more than half of the cases with NNH were idiopathic, where no cause could be identified and in this idiopathic group 65% of babies were receiving exclusive breast feeding. In another report this frequency has been cited as 77.9%.

On the other hand, association between breast feeding and neonatal jaundice has been questioned by others.[11]

In the recent years increased prevalence of breast feeding in conjunction with early discharge practices has increased the risk for marked hyperbilirubinemia in term and near term infants[16]. This has resulted in the potential for bilirubin brain injury in affected infants.[20]

Sex Of The Baby

Several studies[29] in the past had reported increased incidence of NNHB in male babies. Data [3]from India suggests a marginal male preponderance.

Other Risk Factors Include

- Immune or other hemolytic disease
- Previous sibling with jaundice
- Cephalohematoma Or significant bruising
- East Asian race
- Gestational age 35 to 36 weeks
- Hematocrit
- Direct and indirect coomb's test
- SGA /LGA/IUGR
- Maternal infections while pregnancy
- East Asian race
- Family history of G6PD, Spherocytosis
- Birth asphyxia
- Delayed cord clamping

AIMS AND OBJECTIVE :

A) To assess whether umbilical cord bilirubin (UCB) level at delivery predict development of neonatal jaundice in newborn more than 35 weeks.

B) To estimate the development of targeted primary therapy and follow up for early estimation of infants at high risk.

MATERIALS AND METHODS

Place of study

The study was carried out in Hi-tech Medical and hospital, Bhubaneswar

Study Material

The study was conducted in the postnatal ward of the hospital. Neonates born with gestation of >35 weeks at Hi-Tech Medical College & Hospital, Bhubaneswar were considered.

Type of Study

This was a prospective study. All parameters were taken during the hospital stay of the mother and baby which was 5 – 7 days.

Criteria For Selection Of Babies

Live born singleton babies without any congenital anomalies, born at 35 completed weeks or more of gestation and with an Apgar score of eight and above at 1 min of life were included in the study.

Gestational age of newborn babies were determined according to the first day of mother's last menstrual period (by the mother's statement) and were additionally confirmed by the Ballard Scoring System. Babies whose mother could not recall the exact date of last menstrual period were not included in the study

Other exclusion criterias were :

- Respiratory distress
- Clinical or culture proven sepsis.

- Newborn who died during hospital stay.
- Those who needed NICU care due to any reason other than hyperbilirubinemia.
- G-6 PD deficiency.
- Whose parents did not give consent to participate in the study.
- All the newborn babies who satisfied the selection criteria were considered for the study

Method Of Data Collection

Data was collected according to the proforma (attached herewith). Proforma was filled up by interviewing with the mother, by clinical consideration, by examining the baby and by some lab investigations and hospital documents.

Collection Of Blood Sample

Cord bilirubin of neonates >35weeks of gestational age were taken at birth and compared with serum bilirubin (total and direct) at 24hrs and with neonatal jaundice at 3 – 5 days as per NICE (UK National Institute for Health and Care Excellence) guidelines.

Neonates with ABO or Rh incompatibility or hemolysis due to any other cause is taken into account.

Peripheral venous blood sample was drawn at the first appearance of significant clinical icterus according to Kramer's criteria or even early in cases of suspected blood group incompatibility.

Total serum bilirubin value of more than 12.9 mg/100 ml at any time during first week of life was considered as hyperbilirubinemia in the study.

To identify aetiological spectrum, several investigations of baby were done : viz. ABO, Rh typing, DCT, Reticutocyte count, hemoglobin estimation, peripheral smear, hematocrit, G-6 PD screening.

Examination of baby

All babies were examined in naked condition in natural day light for appearance of icterus.

Appropriate treatment in the form of phototherapy or exchange transfusion was given as per standard guidelines and protocols followed by the hospital.

Method Of Bilirubin Estimation

Serum bilirubin estimation was done in the biochemistry department of this hospital. The method applied was Jendrassik and Grof technique.

Statistical Method

The statistical constants have been calculated by standard methods. A receiver operating characteristics (ROC) analysis was calculated to determine optimal cut off value for umbilical cord blood total bilirubin level.

The study was approved by the local ethical committee and informed consent was obtained from all the parents of the newborn babies in the study.

Data collected under the study were scrutinised, coded and entered into the IBM SPSS Statistics, 24.0 software, www.spss.co.in for analysis. The categorical variables like age group, mother blood group, prolonged labour >24 hrs, IAP, leaking PV/PROM/PPROM, gestational age, oligo/poly, indication, mode of delivery, H/O drug intake, euthyroid, GDM/DMT1/T2/PIH/ECLAMPSIA/PREECLAMPSIA, HIV/HBS/VDRL/TORCH, gender of neonates, neonates blood group, phototherapy, DCT, type of feed, sibling H/O phototherapy, birth trauma, delayed cord clamp and complications of neonates were done by using frequency distribution procedure.

Comparison of mean ± SD of cord bilirubin total & direct, 24 hrs serum bilirubin total & direct, 72 hrs serum bilirubin total & direct, haematocrit, APGAR score at 1 & 5 min and gestational age by phototherapy were done by using Independent sample 't' test. Association of mother blood group, Prolonged Labour >24Hrs, IAP, Leaking PV/PROM/PPROM, Oligo/Poly, Indication, Mode of Delivery, H/O Drug Intake, Euthyroid, GDM/DMT1/T2/PIH/ECLAMPSIA/PREECLAMPSIA, Phototherapy, DCT, Type of Feed, Sibling H/O Phototherapy, Birth Trauma and AGA/SGA/LGA/IUGR with cord bilirubin total by using cross tabulation procedure and their association was studied by using Chi-square test of independence. ROC analysis was done for diagnostic efficacy of Cord Bilirubin total, 24 hrs 72 hrs of Serum as a marker of neonatal jaundice in neonates. Cut off value 'p'<0.05 was consider to indicate statistical significance.

RESULTS AND ANALYSIS

5 Observations

The study is about assessing whether umbilical cord bilirubin (UCB) level at delivery predicts the development of neonatal jaundice in newborn with gestational age 35 weeks or more. Data was collected in respect of 102 neonates and the respective mothers. Data analysis and interpretation is presented in this chapter in three sections. The 1st section deals with the profile of mothers of the neonates, the 2nd one presents the profile of neonates and the third one analyses the different clinical parameters in comparision with phototherapy status.

5.1. Profile Of Mothers Of Neonates

5.1.1. age Of Mothers

Maximum proportions of mothers, nearly half are within 26 – 30 years age group. About 1/5th mothers (21.6%) were above the age of 30 years and 29.4% were 25 years or lower. The mean age was 27.7 ± 4.0 years. Table 5.1 depicts the details.

Table 5.1 Age distributions of mothers		
Age of mother's in years	No.	%
≤25	30	29.4
26-30	50	49
>30	22	21.6
Total	102	100
Mean ± SD	27.7 ± 4.0	

5.2 Clinical Profile Of Mothers

Maximum proportions of mothers had B+ blood group (42.2%) followed by O+ blood group (31.4%). Lowest proportions of mothers belonged to AB+ blood group. About a quarter of the mothers (25.5%) had prolonged labour exceeding 24 hours. About 10.8% of mothers had Intra-natal antibiotic prophylaxis. It was found that 87.3% of the mothers did not present leaking PV/PROM/PPROM. Out of the remaining 12.7% who had leaking PV/PROM/PPROM, 8.8% presented the symptoms within ≤ 12 hours while 3.9% beyond 12 hours. The mean gestational age was 38.6 ± 1.8. Details can be seen in **Table 5.2**

No amniotic fluid disorders was found among 83.3% cases, while Oligohydramnios f was found among 14.7%. Amnionitis and Chorioamnionitis were found in 1 case each. **(Table 5.3)**

Indication for LSCS was found among 18.6% cases, out of which 9.8% were MSAF, 1% breech, 4.9% fetal distress, 1% prolonged labour and 2% with both fetal distress and cord around neck **(Table 5.3)**.

Only 2% cases were having normal vaginal delivery and remaining were LSCS. Emergency LSCS was done on 20.6%, while 75.5% were elective LSCS. **(Table 5.3)**

Table 5.2 Clinical profile of mothers (N=102)		
Mother Blood Group	No.	%
A+	20	19.6

B+	43	42.2
AB+	6	5.9
O+	32	31.4
O-	1	1
Prolonged Labour >24Hrs		
No	76	74.5
Yes	26	25.5
IAP		
No	91	89.2
Yes	11	10.8
Leaking PV/PROM/PPROM		
No	89	87.3
≤12 hrs	9	8.8
>12 hrs	4	3.9
Gestational age in weeks	38.6 ± 1.8	

Table 5.3 Oligo/Poly, Indication and Mode of Delivery		
Oligo/Poly	No.	%
NO INDICATION	85	83.3
OLIGOHYDRAMNIONITIS	15	14.7
AMNIONITIS	1	1
CHORIOAMNIONITIS	1	1
Indication		
No	83	81.4
MSAF	10	9.8
Breech	1	1
Fetal Distress	5	4.9
Prolonged Labour	1	1
Fetal Distress, Cord around neck	2	2
Mode of Delivery		
NVD	2	2
EM LSCS	21	20.6
EL LSCS	77	75.5
Total	102	100

Drug Intake, Morbid Conditions And Complications

Drug intake, morbid conditions and complications of mothers of neonates are presented in **Table 5.4**

Most cases did not found to having drug intake (97.1%). Only three cases were found withdrug intake such as calcigard, thyroxine 100 mg. and thyroxine 150 mg. with one case each. Hyperthyroidism was found among 2 cases only. As high as 93 (91.2%) cases did not have morbidity or complications such as GDM/ DMT1/ T2/ PIH/ ECLAMPSIA/ PREECLAMPSIA. Out of 9 cases with complications 2 were PIH, 2 GDM, 2 ECLAMPSIA and 1 case each belonged to ASTHMATIC, GDM & HTN and GDM, ECLAMPSIA. None of the cases had HIV/HBS/VDRL/TORCH.

Table 5.4 Drug Intake, co-morbid conditions and complications		
H/O Drug Intake	No.	%
No	99	97.1
CALCIGARD	1	1
THYROXINE 100	1	1
THYROXINE 150	1	1
THYROID STATUS		
N	100	98
Hyperthyroidism	2	2
GDM/DMT1/T2/PIH/ECLAMPSIA/PREECLAMPSIA		
No	93	91.2
PIH	2	2
GDM	2	2
ASTHMATIC	1	1
ECLAMPSIA	2	2
HTN	1	1
GDM	1	1
HIV/HBS/VDRL/TORCH		
No	102	100
Total	102	100

5.3Profile of neonates

5.3.1 Gender and birth weight of neonates

Male (52.9%) and females (47.1%) are almost evenly balanced in the sample (p=0.621) .The mean birth weight of neonates was 2.68 kg. (Table 5.5)

Table 5.5 Gender of Neonates		
Gender	No.	%
Male	54	52.9
Female	48	47.1
Binomial test 'p' value		
Birth weight	2.68 ± 0.44	

5.3.2Distribution of Blood groups among neonates

O^+ and B^+ are most common blood group among neonates with a share of 36.3% and 32.4% respectively. About $1/10^{th}$ of the neonates had AB^+ blood group (Table 5.6).

Table 5.6 Neonates' blood group		
Neonates' blood group	No.	%
A+	20	19.6
B+	33	32.4
AB+	11	10.8
O+	37	36.3
O-	1	1
Total	102	100

Birth parameters and complications of neonates

Phototherapy treatment was given to 72(70.6%) out of 102 neonates as these neonates had indication of jaundice.

DCT was positive in 24.5% cases and was negative in the remaining 75.5% cases.

About 69.6% neonates were on exclusive breastfeeding, while the remaining were on mixed feeding i.e, the neonates were given other food supplements along with breast feeding.

None of the cases had delayed cord clamping. The body weight appropriate for gestational age was found among 73.5% cases. Nearly $1/5^{th}$ (21.6%) cases had Intrauterine growth retardation (IUGR).

Large for gestational age (LGA), a neonates who is larger than expected for their age and gender, was found among 4.9% cases. History of phototherapy among sibling was found among 51% cases and birth trauma among 15.7%. Table 5.7 and Fig. 5.7 presents the details.

Table 5.7 Birth parameter of neonates		
Phototherapy	No.	%
No	30	29.4
Yes	72	70.6
DCT		
No	77	75.5
Yes	25	24.5
Type of Feed		
Exclusive	71	69.6
Mixed	31	30.4
Sibling H/O Phototherapy		
No	50	49
Yes	52	51
Birth Trauma		
No	86	84.3
Yes	16	15.7
Delayed Cord Clamp		
No	102	100
Yes	0	0
Complications of neonates		
AGA	75	73.5
IUGR	22	21.6
LGA	5	4.9
Total	102	100

5.3.4. Comparison of neonatal parameters by neonataljaundice (phototherapy)

5.3.5. Bilirubin status by neonatal jaundice

Table 5.8 and Fig.5.8 present comparison of cord bilirubin at birth ,and s.bilirubin at 24 hrs, at 72 hrs by the neonatal jaundice receiving phototherapy. Out of 102 neonates 72 had undergone phototherapy for jaundice and 30 did not receive phototherapy. It was found that the mean of cord bilirubin at birth, s. bilirubin at 24 hrs and at 72 hrs , 72 hrs s. bilirubin had significantly higher value for the neonates with phototherapy ($p<0.05$). However, the mean cord bilirubin , 24 hrs s. bilirubin and 72 hrs s. bilirubin direct did not differ significantly between phototherapy and non-phototherapy groups ($p>0.05$).

Table 5.8 Comparison of Bilirubin status by phototherapy

Variables	Phototherapy		Independent sample 't' test 'p' value
	No (N=30)	Yes (N=72)	
	Mean ± SD	Mean ± SD	
Cord Bilirubin Total	1.56 ± 0.63	2.21 ± 0.48	0.000
Cord Bilirubin Direct	0.51 ± 0.33	0.54 ± 0.19	0.468
24 hrs S.Bilirubin Total	5.42 ± 1.89	7.37 ± 2.05	0.000
24 hrs S.Bilirubin Direct	0.57 ± 0.27	0.81 ± 1.16	0.260
72 hrs S.Bilirubin Total	11.66 ± 1.84	16.04 ± 1.81	0.000
72 hrs S.Bilirubin Direct	0.90 ± 1.01	0.83 ± 0.64	0.686

Comparison of hematocrit and APGAR by phototherapy

The mean haematocrit (%) in the phototherapy group was 49.7 ± 5.2% and that in non-phototherapy group was 52.5 ± 7.1% and the difference was not significant (p= 0.053). Similarly mean APGAR 1 min in phototherapy group (8.9 ± 0.4%) did not differ significantly from that of non-phototherapy group (8.9 ± 0.3%) with p =0.965. At APGAR 5 minutes the means are of same values. Table 5.9 presents the details.

Table 5.9 Comparison of hematocrit and APGAR by phototherapy

Variables	Phototherapy		Independent sample 't' test 'p' value
	No (N=30)	Yes (N=72)	
	Mean±SD	Mean±SD	
Hematocrit In %	49.7 ± 5.2	52.5 ± 7.1	0.053
APGAR 1 Min	8.9 ± 0.4	8.9 ± 0.3	0.965
APGAR 5 Min	9.0 ± 0.0	9.0 ± 0.0	*

* 'p' value cannot be computed because the standard deviations of both groups are 0.

Comparison Of Gestational Age By Phototherapy

Table 5.10 and Fig. 5.10 present the comparison of gestational age by phototherapy. The mean gestational age of pregnancy in the phototherapy group was 38.7 ± 1.9 weeks and that in non-phototherapy group of neonates was 38.5 ± 1.8 weeks. The difference was not significant (p= 0.653).

Table 5.10 Comparison of gestational age by phototherapy

Phototherapy	N	Gestational age in weeks		Independent sample 't' test 'p' value
		Mean	SD	
No	30	38.7	1.9	0.635
Yes	72	38.5	1.8	

5.3.7 Cord Bilirubin Total Of Serum As A Marker Of Neonatal Jaundice

Table 5.11 and Fig.5.11-13 present the ROC analysis for evaluating the cord bilirubin total of serum as a marker of neonatal jaundice. Total cord bilirubin values at three time periods have been taken- after birth, 24 hours and 72 hours of birth have been observed. Area under the ROC curve was 0.797 (CI: 0.694 to 0.900), 0.768 (CI: 0.667 to 0.863) and 0.953 (CI: 0.913 to 0.992) for cord bilirubin total at birth, 24 hrs 72 hrs of birth respectively. The AUC for cord bilirubin was found to be significant for all the three time points ($p<0.001$).

The cut off value for cord bilirubin at birth as a marker of neonatal jaundice was >1.64 with sensitivity 90.28, 95% CI (81.0-96.0), specificity 60, 95% CI (40.6-77.3), positive likely hood ratio 2.26, 95% CI (1.45-3.52) and negative likely hood ratio 0.16, 95% CI (0.076-0.35).

The cut off value for cord bilirubin at 24 hours of birth as a marker of neonatal jaundice was >5.81with sensitivity >5.81, specificity 66.67, 95% CI (47.2-82.7), positive likely hood ratio 2.42, 95% CI (1.44-4.06) and negative likely hood ratio 0.16, 95% CI (0.076-0.35).

The cut off value for cord bilirubin at 72 hours of birth as a marker of neonatal jaundice was >14.3with sensitivity 86.11, 95% CI (75.9-93.1), specificity 96.67, 95% CI (82.8-99.9), positive likely hood ratio 25.83, 95% CI (3.75-177.85) and negative likely hood ratio 0.14, 95% CI (0.081-0.26).

The cord bilirubin at 3 time points can provide efficient diagnostic indication for neonatal jaundice.

Table 5.11 Cord Bilirubin total, 24 hrs 72 hrs of Serum as a marker of neonatal jaundice in neonates

Parameters	Cord Bilirubin Total	24 hrs S.Bilirubin Total	72 hrs S.Bilirubin Total
Area under the ROC curve (AUC)	0.797	0.768	0.953
95% Confidence interval b	0.694 to 0.900	0.667 to 0.863	0.913 to 0.992
Significance level P (Area=0.5)	<0.0001	<0.0001	<0.0001
Associated criterion	>1.64	>5.81	>14.3
Sensitivity	90.28, 95% CI(81.0-96.0)	80.56, 95% CI (69.5-88.9)	86.11, 95% CI (75.9-93.1)
Specificity	60, 95% CI (40.6-77.3)	66.67, 95% CI (47.2-82.7)	96.67, 95% CI (82.8-99.9)
Positive Likelihood Ratio	2.26, 95% CI (1.45-3.52)	2.42, 95% CI (1.44-4.06)	25.83, 95% CI (3.75-177.85)
Negative Likelihood Ratio	0.16, 95% CI (0.076-0.35)	0.29, 95% CI (0.17-0.50)	0.14, 95% CI (0.081-0.26)

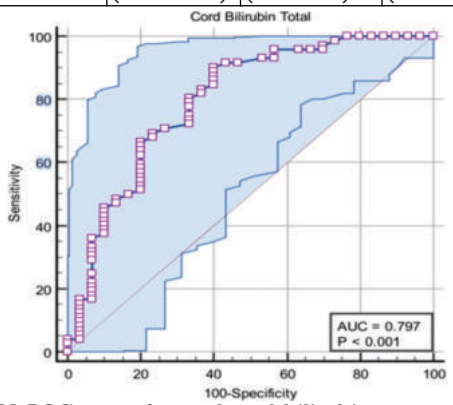

Fig 5.11 ROC curve for total cord bilirubin as a marker of neonatal jaundice

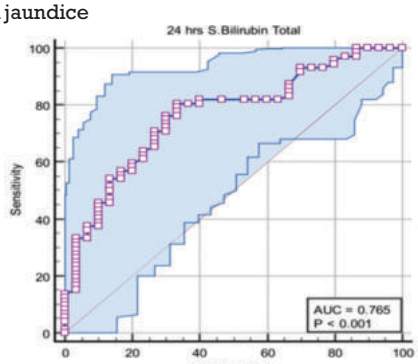

Fig 5.12 ROC curve for total 24 hrs S. bilirubin as a marker of neonatal jaundice

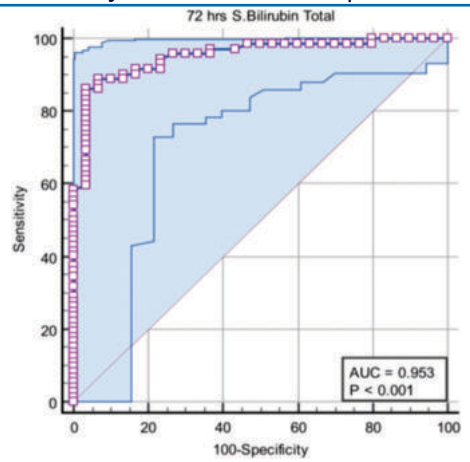

Fig 5.13 ROC curve for total 72 hrs S. bilirubin as a marker of neonatal jaundice

Association Of Maternal Clinical Factors With Total Cord Bilirubin

Association of maternal clinical factors with total cord bilirubin is presented in table 5.12. Prolonged Labour >24Hrs, IAP, Leaking PV/PROM/PPROM, Oligo/Polyhydraminos , mode of Delivery, H/O Drug Intake, mother's clinical status did not have significant association with neonatal jaundice (p>0.05).

Table 5.12 Association of maternal clinical factors with total cord bilirubin

Variables	Classification	Cord Bilirubin Total				Total (N=102)		p' value
		≤1.64 (N=25)		>1.64 (N=72)				
		No.	%	No.	%	No.	%	
Mother Blood Group	A+	5	20	15	19.5	20	19.6	0.603*
	B+	9	36	34	44.2	43	42.2	
	AB+	3	12	3	3.9	6	5.9	
	O+	8	32	24	31.2	32	31.4	
	O-	0	0	1	1.3	1	1	
Prolonged Labour >24Hrs	No	19	76	57	74	76	74.5	0.844*
	Yes	6	24	20	26	26	25.5	
IAP	No	22	88	69	89.6	91	89.2	0.822*
	Yes	3	12	8	10.4	11	10.8	
Leaking PV/PROM/PPROM	No	24	96	65	84.4	89	87.3	0.292*
	≤12 hrs	1	4	8	10.4	9	8.8	
	>12 hrs	0	0	4	5.2	4	3.9	
Oligo/Poly	No	21	84	64	83.1	85	83.3	0.312*
	OLIGO	3	12	12	15.6	15	14.7	
	Amnionitis	0	0	1	1.3	1	1	
	Chorioamnionitis	1	4	0	0	1	1	
Indication	No	19	76	64	83.1	83	81.4	0.418*
	MSAF	3	12	7	9.1	10	9.8	
	Breech	0	0	1	1.3	1	1	
	Fetal Distress	3	12	2	2.6	5	4.9	
	Prolonged Labour	0	0	1	1.3	1	1	
	Fetal Distress, Cord around neck	0	0	2	2.6	2	2	
Mode of Delivery	NVD	0	0	2	2.6	2	2	0.685*
	EM LSCS	6	24	15	19.5	21	20.6	
	EL LSCS	19	76	58	75.3	77	75.5	
	PREV LSCS	0	0	2	2.6	2	2	
H/O Drug Intake	No	24	96	75	97.4	99	97.1	0.292*
	CALCIGARD 10	1	4	0	0	1	1	
	THYROXINE 100	0	0	1	1.3	1	1	
	THYROXINE 150	0	0	1	1.3	1	1	
Euthyroid	N	25	100	75	97.4	100	98	0.416*
	HYPER	0	0	2	2.6	2	2	
GDM/DMT1/T2/PIH/ECLAMPSIA/PRE ECLAMPSIA	No	20	80	73	94.8	93	91.2	0.171*
	PIH	1	4	1	1.3	2	2	
	GDM	1	4	1	1.3	2	2	
	ASTHMATIC	1	4	0	0	1	1	
	ECLAMPSIA	1	4	1	1.3	2	2	
	GDM, HTN	1	4	0	0	1	1	
	GDM, Eclampsia	0	0	1	1.3	1	1	
Gestational age in weeks	Mean ± SD	38.5 ± 1.7		38.6 ±1.9		38.6 ± 1.8		0.809#
* Chi-square test 'p' value								
# Independent sample 't' test 'p' value								

5.3.10Association of neonates' clinical factors with total cord bilirubin

The cut off point for cord bilirubin total at birth was found to be >1.64. The table 5.13 and Fig. 5.14 present association of clinical factors of neonates with total cord bilirubin, which is classified into two groups – >1.64 and ≤1.64.

In the phototherapy group, out of 72 cases, 90.3% had cord bilirubin total value more than 1.64, while the corresponding proportion was only 40.3% among the 30 cases of non-phototherapy group and the association was found significant (p=0.000).

Among the 25 cases with DCT positive, 96.0% had cord bilirubin total value more than 1.64, while the corresponding proportion was only 68.8% among the 77 cases with DCT negative and the association was found significant (p=0.006).

Among the 71 cases with exclusive breast feeding, 69.0% had cord bilirubin total value more than 1.64, while the corresponding proportion among 31 mixed feeding group was 90.3% and the association was found significant (p=0.021).

Among the 16 cases of birth trauma, all had cord bilirubin total value more than 1.64, while the corresponding proportion among 86 without birth trauma was 70.9% and the association was found significant (p=0.013).

Birth complications like AGA, IUGR and LGA did not have significant association with cord bilirubin total (p=0.925)

Table 5.13 Association of neonates' clinical factors with total cord bilirubin

Variables	Classification	Cord Bilirubin Total				Total (N=102)		Chi-square 'p' value
		≤1.64 (N=25)		>1.64 (N=72)				
		No.	%	No.	%	No.	%	
Phototherapy	No	18	60.0	12	40.0	30	100	0.000
	Yes	7	9.7	65	90.3	72	100	
DCT	No	24	31.2	53	68.8	77	100	0.006
	Yes	1	4.0	24	96.0	25	100	
Type of Feed	Exclusive	22	31.0	49	69.0	71	100	0.021
	Mixed	3	9.7	28	90.3	31	100	
Sibling H/O Phototherapy	No	18	36.0	32	64.0	50	100	0.008
	Yes	7	13.5	45	86.5	52	100	
Birth Trauma	No	25	29.1	61	70.9	86	100	0.013
	Yes	0	0	16	100.	16	100	
AGA/SGA/LGA/IUGR	AGA	18	24.0	57	76.0	75	100	0.925
	IUGR	6	27.3	16	72.7	22	100	
	LGA	1	20.0	4	80.0	5	100	

In a study done by Eshwara Chary et al.[12]to identify the newborns at risk for developing significant hyperbilirubinemia using cord blood serum bilirubin levels, out of 282 healthy term newborns 51 (18.09%) developed significant hyperbilirubinemia. In their study, the umbilical cord bilirubin cut off point was 2 mg/dl which had good sensitivity (94.12), specificity (90.9%), positive predictive value (69.57%) and negative predictive value (98.59%).

Similarly Amar Taksande et al.[13] in their study on healthy term neonates for prediction of neonatal hyperbilirubinemia, concluded that the cord blood bilirubin level of more than 2 mg/dl had the highest sensitivity (89.5%), and also showed this critical bilirubin level had a very high (98.7%) negative predictive value and a low (38.6%) positive predictive value.

Ramamoorthy K et al in their study revealed the cord bilirubin level of >2 mg/dl had the highest sensitivity (93.3%) and this critical bilirubin level had a very high (98.9%) negative predictive value and fairly low (23.3%) positive predictive value. As per the findings of this study, a critical cut off level of cord bilirubin was 2 mg/dl predicted 90% of the newborns who developed jaundice. However, the cord bilirubin level of <2 mg/dl did not completely exclude the development of significant hyperbilirubinemia; only 2.05% of the newborns with cord bilirubin levels of <2 mg/dl developed jaundice. 98.9% negative predictive value in the present study suggested that measurement of cord serum bilirubin can help in identify those newborns that are unlikely to require further evaluation and intervention. [14]

Alpay et al observed that a serum bilirubin >6 mg/dl on the first day of life had 90% sensitivity of predicting a subsequent TSB >15 mg/dl between 2nd and 5th day of life. At this critical serum bilirubin value, the negative predictive value was 97%. No cases with TSB of <6 mg/dl in first 24 hours required phototherapy treatment value of measuring cord bilirubin concentration in ABO- incompatibility had been investigated by Riesenberg et al who found that all infant with cord bilirubin level is higher than 68 mmol/l and development severe jaundice .[15]

Trisiah et al reported in their study that all the risk of significant hyperbilirubinemia was 1.6% in cases whose bilirubin level was <5 mg/dl at 24 hours of life, whereas that risk was 6.6% in cases whose bilirubin level was 5 mg/dl at 24 hrs of life. The maternal and umbilical cord bilirubin concentration at delivery, a yellow skin colour during the first 24 hrs or postnatal life and carbon monoxide excretion are all associated with the later development of neonatal jaundice in healthy mature newborn infant. The incidence of significant hyperbilirubinemia depends on regional variations, ethnic makeup of the population, laboratory variability in the measurement of bilirubin and the incidence of breastfeeding. 8 In the present study group, there were no significant hyperbilirubinemia with respect to these factors (such as hemoglobin level, haematocrit level, gender, delivery route, birth weight and gestational age) that might be associated with the risk of hyperbilirubinemia..[16]

Trisiah et al reported in their study, with the 1st day bilirubin level of >4.5 mg/dl showed that it has a sensitivity 90%, specificity 71.9%, positive predictive value 50% and negative predictive value of 96.8% in predicting neonatal hyperbilirubinemia. In this study, 1st day or 24 hrs bilirubin levels ≥5 mg/dl found to be used as an early predictor of neonatal hyperbilirubinemia.[16]

Randev et al found 24 neonates among 200 enrolled (i.e., 12%) developed hyperbilirubinemia. The mean first day TSB value in the neonates who subsequently developed hyperbilirubinemia was 7.716 mg/dl as compared to a value of 5.154 mg/dl in those who did not. Using Receiver operating characteristic (ROC) curve analysis, a value of 6.4 mg/dl (first day TSB) was determined to have the best predictive ability for subsequent hyperbilirubinemia with a sensitivity of 87.5%, specificity of 80.11%, positive predictive value of 37.5% and a negative predictive value of 97.92%.[17]

DISCUSSION

In a study done by Eshwara Chary et al.[12]to identify the newborns at risk for developing significant hyperbilirubinemia using cord blood serum bilirubin levels, out of 282 healthy term newborns 51 (18.09%) developed significant hyperbilirubinemia. In their study, the umbilical cord bilirubin cut off point was 2 mg/dl which had good sensitivity (94.12), specificity (90.9%), positive predictive value (69.57%) and negative predictive value (98.59%).

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Ramamoorthy K et al in their study revealed the cord bilirubin level of >2 mg/dl had the highest sensitivity (93.3%) and this critical bilirubin level had a very high (98.9%) negative predictive value and fairly low (23.3%) positive predictive value. As per the findings of this study, a critical cut off level of cord bilirubin was 2 mg/dl predicted 90% of the newborns who developed jaundice. However, the cord bilirubin level of <2 mg/dl did not completely exclude the development of significant hyperbilirubinemia; only 2.05% of the newborns with cord bilirubin levels of <2 mg/dl developed jaundice. 98.9% negative predictive value in the present study suggested that measurement of cord serum bilirubin can help in identify those newborns that are unlikely to require further evaluation and intervention. [14]

Alpay et al observed that a serum bilirubin >6 mg/dl on the first day of life had 90% sensitivity of predicting a subsequent TSB >15 mg/dl between 2nd and 5th day of life. At this critical serum bilirubin value, the negative predictive value was 97%. No cases with TSB of <6 mg/dl in first 24 hours required phototherapy treatment value of measuring cord bilirubin concentration in ABO- incompatibility had been investigated by Riesenberg et al who found that all infant with cord bilirubin level is higher than 68 mmol/l and development severe jaundice .[15]

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Randev et al found 24 neonates among 200 enrolled (i.e., 12%) developed hyperbilirubinemia. The mean first day TSB value in the neonates who subsequently developed hyperbilirubinemia was 7.716 mg/dl as compared to a value of 5.154 mg/dl in those who did not. Using Receiver operating characteristic (ROC) curve analysis, a value of 6.4 mg/dl (first day TSB) was determined to have the best predictive ability for subsequent hyperbilirubinemia with a sensitivity of 87.5%, specificity of 80.11%, positive predictive value of

37.5% and a negative predictive value of 97.92%.[17]

Our study showed significant association between umbilical cord blood bilirubin level and hyperbilirubinemia. In this study using the critical value of 1.6 mg/dl or more, umbilical cord blood bilirubin can predict the newborns who can develop significant hyperbilirubinemia with sensitivity of 90.28, 95% CI (81.0-96.0) and specificity of 60, 95% CI (40.6-77.3) . At this critical level of 1.6mg/dl the positive predictive value was ---------- and the negative predictive value was ---------

SUMMARY & CONCLUSION

Based on our results, we conclude that significant positive correlation is present between umbilical cord blood bilirubin level and significant hyperbilirubinemia. Cut off umbilical cord blood bilirubin level of 1.6mg/dl in healthy term neonate can predict significant hyperbilirubinemia with high sensitivity and specificity. Neonates with umbilical cord bilirubin level < 1.6 mg/dl are at low risk of significant hyperbilirubinemia and can be discharged early from hospital. Umbilical cord blood bilirubin level can be used as screening tool for development of significant hyperbilirubinemia.

Limitation

Limitations of the study were, only more than 35 weeker healthy neonates were taken for the study. Since the peak bilirubin level reached on 1st and 2nd postnatal days, babies are followed till 5 days of delivery. In view of early discharge of the babies delivered vaginally, increased representation of babies extracted by caesarean section were taken.
Our study sample was also limited

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