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Evaluation of critical cord blood bilirubin level as a predictor of significant hyperbilirubinemia in term newborns

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Abstract
Background: *Jaundice is the commonest abnormal physical finding during first week of life. Over two-thirds of newborn babies develop clinical jaundice and by adult standards, almost all newborn babies are jaundiced. In term babies, physiological jaundice appears between 36-72 hours of age while pathological jaundice appears within 24 hours of life. Serum total bilirubin concentrations have been defined as nonphysiologic if the concentration exceeds 5 mg/dl on the first day of life in a term neonate, 10 mg/dl on the second day, or 12 to 13 mg/dl thereafter.*
Objectives: *To evaluate the critical cord blood bilirubin level as a predictor of significant hyperbilirubinemia and the occurrence of hyperbilirubinemia in term newborns.*
Materials and Methods: *In a cross-sectional study conducted over 2 years in a tertiary care referral hospital in Manipur, India, 300 newborns without complications were selected and the cord blood bilirubin estimation was done at birth and serum bilirubin at 48 hours of life.*
Results: *There were no significant differences between the cases who cord bilirubin level < 3 mg/dl and > 3 mg/dl with respect to various factors that may be associated with the risk of hyperbilirubinemia, such as gender, gestational age, birth weight and oxytocin used. Mean cord bilirubin level was 2.01 mg/dl. Mean total bilirubin on 48-hour post- natal day was 10.06 mg/dl. There was a positive correlation between cord bilirubin and 48-hour postnatal day serum bilirubin. The correlation between cord bilirubin and development of significant jaundice in the first three days is statistically significant.*
Conclusions: *Using cord bilirubin level of ≥ 3 mg/dl, hyperbilirubinemia can be predicted with sensitivity of 100%, specificity of 99%, positive predictive value of 66% and negative predictive value of 100%.*
Keywords: *Jaundice, term newborns, serum bilirubin.*

Introduction

Jaundice is the commonest abnormal physical finding during first week of life. The clinical jaundice manifests on the face at a serum bilirubin level of 5 mg/dl (1mg = 17 μmoles/l), on trunk at 10-15 mg/dl, and on soles or palms at more than 15 mg/dl. Jaundice occurs in both physiological and pathological processes in newborns. Jaundice due to physiological immaturity of newborn babies is seen in 60% of term and 80% of preterm babies. In term babies, physiological jaundice appears between 36-72 hours of age while

pathological jaundice appears within 24 hours of life.[1] Serum total bilirubin concentrations have been defined as nonphysiologic if the concentration exceeds 5 mg/dl on the first day of life in a term neonate, 10 mg/dl on the second day, or 12 to 13 mg/dl thereafter.[2]

Early hospital discharge has had the implication of re-examining the approach towards neonatal jaundice, taking into consideration the bilirubin level present in the first 24 hours to 48 hours of life as a means of predicting hyperbilirubinemia. A reliable clinically evaluated method for estimation of the risk of bilirubin dependent brain damage is still lacking. Physical examination is not a reliable measure of serum bilirubin. Under these circumstances, it would be desirable to be able to predict the risk of hyperbilirubinemia in order to implement early treatment and minimize the risk of bilirubin dependent brain damage.[3]

Bilirubin induced neurological dysfunction does not occur in the absence of hyperbilirubinemia. Kernicterus is a rare but devastating condition that is not extinct. It is usually associated with complicating conditions such as iso-immunization or other causes of hemolysis, prematurity, sepsis, other illness or constitutional defects in hepatic bilirubin clearance.[4] However, as has been documented in several recent reports, it occasionally occurs in healthy breast or bottle fed infants born at or near term in the absence of diagnosed complicating factor.[5-9]

The gold standard for deciding therapy to prevent encephalopathy continues to be serum bilirubin levels for want of better parameters. The clinical practice of reporting bilirubin on the basis of age in days was misleading and confusing. It should be remembered that the bilirubin rises by the "hours" of life and hence the time of sampling must be as 'hours of life' and not 'day of life'.

Hour specific percentile charts based on serum bilirubin at different postnatal ages have been developed. They show that subsequent hyperbilirubinemia can be predicted with reasonable accuracy by plotting for specific bilirubin on these charts.[10] There is paucity of literature on this concept of prediction of hyperbilirubinemia.

The present study was carried out to evaluate the predictive value of umbilical cord bilirubin level at birth for identifying term neonates at risk for subsequent hyperbilirubinemia.

Objectives

To evaluate the critical cord blood bilirubin level as a predictor of significant hyperbilirubinemia and the occurrence of hyperbilirubinemia in term newborns.

Materials and Methods

Study Design: Cross - sectional study.

Study Setting: Labour Room and Post-Natal Ward, Regional Institute of Medical Sciences, Imphal.

Study Period: September 2015 to August 2017

Study Population: Newborns without complications delivered at Regional Institute of Medical Sciences, Imphal, Manipur.

Inclusion Criteria
  a. Gestational age > 37 weeks to< 42 weeks
  b. Birth weight > 2500 grams

Exclusion Criteria
  a) Rh incompatibility
  b) ABO incompatibility
  c) Newborns with obvious life threatening congenital malformation [Tracheo-oesophagealfistula (TOF), anorectal malformation]
  d) History of intake of drugs in mother affecting fetal liver e.g. sulphonamides, nitrofurantoin, antimalarial drugs.

Sampling Design

The neonates fulfilling the above criterion were taken into consideration for the study. In the Labour room, the cord blood of the neonates was taken at birth for bilirubin level estimation. In the Post-Natal Ward, the venous blood of the neonates was taken at 48 hours of life for bilirubin estimation.

Sample Size[11]

Sample size was calculated based on the previous study for prediction of the development of neonatal hyperbilirubinemia by increased umbilical cord bilirubin by Taksande A et al.[12]

The following diagnostic formula is being used:

N = Z2 x Sn (100 – Sn) = 3.84 (89.5) (10.5) = 322
P x E2 0.14 x (8.95)2

Where: N = sample size = 322

Z = 95% of confident value = 1.96

Sn= sensitivity = 89.5%

P = prevalence = 14%

E = 10% relative error = 10% of sensitivity = 8.95%

Study variables

a) Blood group of mother and newborn baby. If blood group incompatibility is found, then hemoglobin, peripheral smear, reticulocyte count and direct coombs test was done.
b) Sex of the neonates
c) Gestational age
d) Mode of delivery

Outcome variables

a) Cord blood bilirubin of newborn at birth
b) Serum bilirubin of newborn at 48 hours of life

Study Procedure

After taking informed consent from the parents of the neonates, the cord blood bilirubin estimation was done at birth and serum bilirubin level was done at 48 hours of life. The cord and serum bilirubin estimation was done using Modified Jendrassic and Grof method, a colorometric method for estimation of direct and total bilirubin level. All the neonates were observed for the development of jaundice for at least 5 days.

Study tools

The study tool that were used:

Auto Analyser – RX Series BR 3859, Randox Laboratories Limited, United Kingdom, Oct-2009

Working definition

Neonatal hyperbilirubinemia is defined as significant when serum bilirubin level is more than or equal to15 mg/dl.

Data collection

In all the newborns, relevant information was collected in a pre-designed proforma containing information's on

a. Particulars of the child
b. Baby's birth history
c. Apgar score
d. Family history
e. General physical examination
f. Antenatal and Perinatal history
g. Present obstetrics history
h. Investigations

A checklist was maintained for recording cord blood bilirubin and venous blood bilirubin levels.

Statistical analysis

This study is a cross-sectional study. Data was checked for completeness and consistency. Data was entered and analysed using SPSS version 21 for window. Descriptive statistics like age, bilirubin level, etc. was presented as Mean and Standard Deviation, while sex, mode of delivery, etc. was presented as percentage. Receiver operating characteristics (ROC) curve was used to determined Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value. P value < 0.05 was taken as significant.

Ethical approval

Ethical approval was obtained from the institutional ethical committee, RIMS, Imphal, before beginning the study. Consent from the participating individual's parents was obtained and recorded as shown in Performa (Annexure-I). Confidentiality was maintained.

Results and Observations

Figure 1 shows the predominant blood group among the mothers to B type with 41.3% followed by the A type (26.7%), O type (24.7%) and AB type (7.3%).
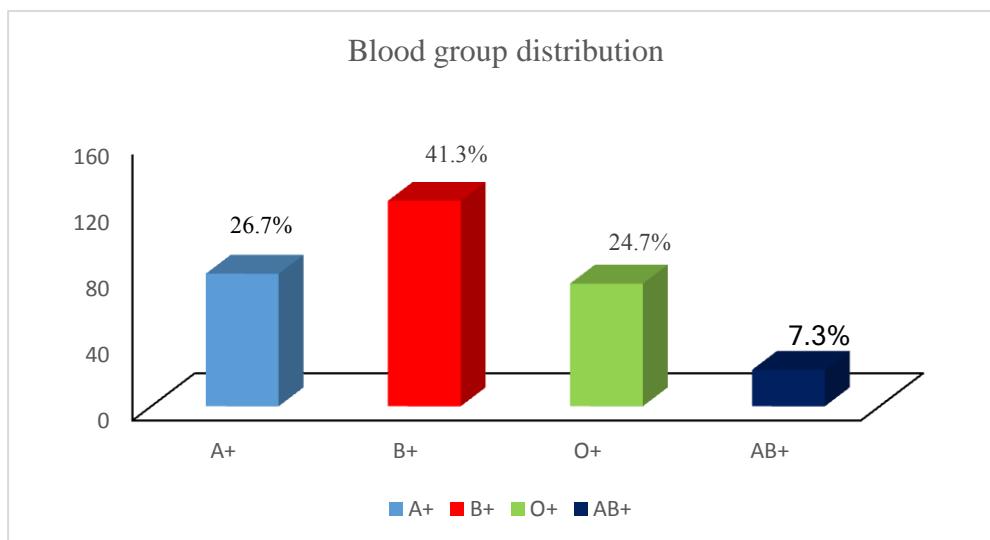
Figure 1: Bar diagram showing distribution of maternal blood group

Figure 2 shows that only 4 (1.3%) of the neonates had a positive history of neonatal jaundice in previous siblings.
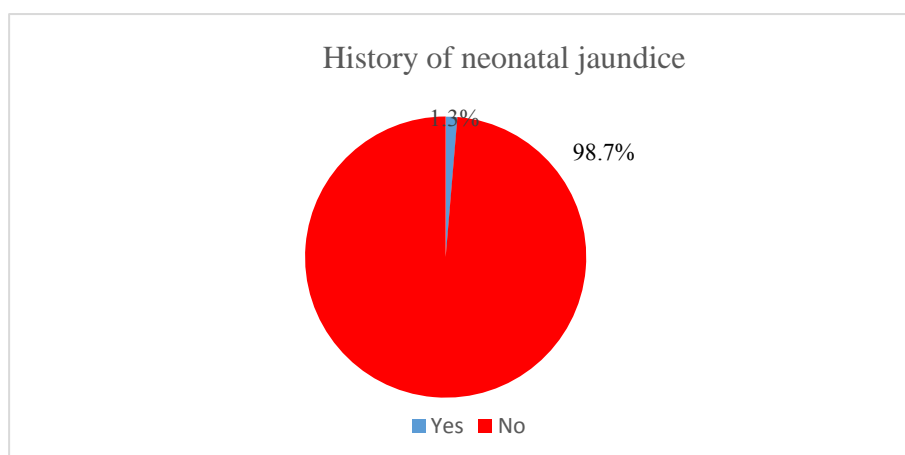

Figure 2: Pie diagram showing history of neonatal jaundice in previous siblings

Table 1 shows that 1.4 % of newborns developed jaundice due to oxytocin induction and 1.2 % of newborns developed jaundice without oxytocin induction

Table 1: Effect of oxytocin induction on jaundice

Oxytocin Induction	Newborn		Jaundice	
	Number	Percentage	Number	Percentage
Yes	140	46.7	2	1.4
No	160	53.3	2	1.2

Table 2 shows that the mean cord bilirubin level was 2.01 mg/dl (range: 0.60- 4.40, SD- 0.45). There was an increase in serum bilirubin level on each day the mean total bilirubin on 48 hours post-natal day was 10.06 mg/dl (range: 3.40-16.80, SD- 2.16).

The mean cord hemoglobin was 15.47 gm% (range: 12.40- 20.00, SD- 1.21) and the 48 hours post natal day mean hemoglobin was 14.43gm% (range: 12.50- 18.00, SD-1.15).

The mean cord PCV was 43.55% (range: 32.50-60.00, SD- 3.85) and the 48 hours post natal day mean PCV was 42.54% (range: 34.00- 55.00, SD-3.34).

Table 2: Bilirubin, Hemoglobin and PCV profile of study population

Parameters	Minimum	Maximum	Mean ± SD	p value
Cord blood Total Bilirubin at birth	0.60	4.40	2.01 ± 0.45	**0.041***
48 hours Total Bilirubin	3.40	16.80	10.06 ± 2.16	**0.036***
Hemoglobin	12.40	20.00	15.47 ± 1.21	0.073
PCV	32.50	60.00	43.55 ± 3.85	0.17
48 hours Hemoglobin	12.50	18.00	14.43 ± 1.15	0.23
48 hours PCV	34.00	55.00	42.54 ± 3.34	0.18

*p value ≤ 0.05: significant

Table 3: Diagnostic predictability of cord blood total bilirubin of > 3 mg/dl for hyperbilirubinemia at 48 hours -- In the present study probability that a neonate with cord bilirubin higher than 3 mg/dl would later develop hyperbilirubinemia (Positive Predictive Values) was 66 %. The negative predictive value of the cord bilirubin lower or equal to 3 mg/dl was 100%. If a neonate becomes hyperbilirubinemic, the probability that the cord bilirubin was higher than 3 mg/dl was 100% (Sensitivity). The probability that the cord bilirubin was lower or equal to 3 mg/dl was 99 % (Specificity) in a non hyperbilirubinemic neonate. The correlation between cord bilirubin and development of significant jaundice in the first three days is statistically significant (p value < 0.05).

Table 3: Diagnostic predictability of cord blood total bilirubin of > 3 mg/dl for hyperbilirubinemia at 48 hours

Diagnostic statistics	
True positive	4
False positive	2
False negative	0
True Negative	294
Sensitivity (%)	100
Specificity (%)	99
PPV (%)	66
NPV (%)	100
Accuracy (%)	99.3

Discussion

Serum bilirubin levels are usually 1-3 mg/ dl at birth and rise at the rate of less than 5 mg/ dl per day, peaking at 2-3 days in term neonates. Our study hypothesis was that a high serum bilirubin level at birth would also predict a high peak later in life. Our aim was to quantify the relationship between Cord blood bilirubin with peak serum bilirubin levels of the first five days. We chose cord blood estimation for initial serum bilirubin estimation because it is a non-invasive way and the results are available within few hours after birth.[13]

The presence of excessive jaundice for age is often missed clinically, which means that the trigger for measuring the first serum bilirubin level and electing subsequent recommendation is not set. This is a potentially a serious problem. Variability in the time of appearance of jaundice from newborn to newborn and in the ability of the professionals to see jaundice and estimate its severity, coupled with the considerable range of TSB values associated with its cephalo-caudal progression, have been the subject of articles spanning nearly 60 years. Even in the landmark Bhutani et al study, with health care providers sensitized to the significance of clinical jaundice, there were several instances when its early appearance was missed (often attributable to confounding skin colour). Additionally, in most of the recently reported healthy term newborns who developed kernicterus, significant jaundice was almost certainly present before the first hospital discharge, judging from the height of TSB for age in hours at readmission. Either the early icterus has not been noted or its pathologic intensity for postnatal age was not appreciated.[14]

Currently we do not have a reliable method of anticipating such levels of hyperbilirubinemia. It is possible that closer, and more frequent, follow up after birth and discharge from the hospital might prevent some of these unfortunate outcomes, but rare, sporadic cases of kernicterus may not be preventable unless we adopt an approach to surveillance of the newborn that is substantially more rigorous than has been practiced. The feasibility, costs, risks and benefits of such an approach need to be determined.

Umbilical cord blood collection is not associated with any pain. Furthermore, most important is that the data are available immediately after birth. The babies at risk for developing hyperbilirubinemia can be detected at birth in a non-invasive way if the neonate leaves the hospital within the first few postnatal days. The use of Cord blood bilirubin values may help to predict infants with low risk for hyperbilirubinemia and minimise an unnecessary prolongation of hospitalization. Keeping these factors in consideration our study was conducted on term healthy neonates with non-haemolytic jaundice. The outcome was hyperbilirubinemia. We have considered peak

serum bilirubin level >15 mg/dl at 48 hours of age as significant hyperbilirubinemia since specific treatment is considered at or above this level.

Table 4: Comparison of incidence of hyperbilirubinemia

Studies	Year	No. of cases	Incidence of hyperbilirubinemia
Palmer et al[42]	1983	41057	10.70 %
Phuapradit et al[37]	1993	7644	8.35 %
Awasthi et al[34]	1998	274	12.80 %
Alpay et al[32]	2000	498	12.05 %
Agarwal et al[31]	2002	213	10.30 %
Knupfer M et al[28]	2005	1100	10.60 %
Randew S et al[24]	2010	200	12 %
Present study	2017	300	1.3 %

Incidence of hyperbilirubinemia varies from 1.3% to 12.8% in various studies. Incidence of hyperbilirubinemia in the present study is 1.3% which is least among all the studies because our study group consisted of neonates with no risk factors.

Table 5: Comparison of cord serum bilirubin and significant jaundice

Studies	Year	No. of cases	Umbilical cord bilirubin	Incidence of hyperbilirubinemia
Rosenfeld J et al[41]	1986	-	< 2mg	4%
			> 2mg	25%
Knudsen et al[15]	1989	291	< 1.17mg	2.9%
			> 2.34mg	85%
Rataj et al[36]	1994	800	≤ 1mg%	2.4%
			> 2.5mg%	89%
Suchonska B et al[29]	2004	-	< 1mg%	0%
Bernaldo et al[4]	2004	380	≥ 2mg%	53%
Knupfer et al[28]	2005	1100	< 1.17mg	0%
			1.17 – 1.75mg	0.30%
			1.75 – 2.34mg	3.4%
			> 2.34mg	8.6%
Present study	2017	300	≤ 3mg	0%
			> 3mg	1.3%

Other studies also reported the relation between raising levels of cord bilirubin and increased incidence of significant hyperbilirubinemia in later life. Raised cord blood bilirubin in ABO or non-ABO situation indicates ongoing in uterohemolysis. These babies are more likely to develop hyperbilirubinemia.

In the present study using serum bilirubin levels ≥ 3 mg/dL in the cord blood, hyperbilirubinemia could be predicted with sensitivity of 100%, specificity of 99 %, positive predictive value of 66 % and Negative predictive value of 100%. The correlation between cord bilirubin and development of significant jaundice in the first three days is statistically significant (p value < 0.05).

Conclusion

The study group consisted of 320 full term neonates delivered in RIMS, Imphal, of which 20 full term neonates were excluded due to non-compliance. Cord blood bilirubin and total serum bilirubin at 48 hours of age was estimated for all neonates. For the first five postnatal days, all these babies in the study group were followed up daily for clinical assessment of icterus. Incidence of significant hyperbilirubinemia (TSB >15 mg/ dl at 48 hours of age) in our study population is 1.3 %. There was uniform sex distribution in the study group.

There were no significant differences between the cases who had cord bilirubin level < 3 mg/dl and > 3 mg/dl with respect to various factors that may be associated with the risk of hyperbilirubinemia, such as gender, gestational age, birth weight and oxytocin used. Mean cord bilirubin level was 2.01 mg/dl. Mean total bilirubin on 48-hour post-natal day was 10.06 mg/dl. There was a positive correlation between cord bilirubin and 48-hour postnatal day serum bilirubin.

Using cord bilirubin level of ≥ 3 mg/dl, hyperbilirubinemia can be predicted with sensitivity of 100%, specificity of 99%, positive predictive value of 66% and negative predictive value of 100%.

Healthy term babies without Rh and ABO incompatibility with cord blood bilirubin ≤ 3 mg/dl are unlikely to require further evaluation and intervention hence these newborns can be discharged with assurance to parents. Babies with cord blood bilirubin level≥ 3 mg/dl should be followed more frequently.

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