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Early Prediction of Significant Neonatal Hyperbilirubinemia using Serum Bilirubin Levels in Healthy term & near term Newborns, Gujarath, India.

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Abstract

Significant neonatal hyperbilirubinemia is the most common cause of readmission after early discharge from hospitals in healthy term neonates. This prospective cohort study is designed to identify those at risk by serially measuring the serum bilirubin values from day 1 to 5 for prediction of significant neonatal hyperbilirubinemia.

Objectives: To determine the 1st & 2nd day TSB values which predict the development of significant neonatal hyperbilirubinemia subsequently in healthy term/ near term newborns.

Materials and Methods: 320 healthy term low risk term/ near term neonates were sampled for TSB daily from day 1 to day 5 of life. TSB >15mg/dl was defined as significant hyperbilirubinemia.

Results: 31(9.6%) babies developed significant hyperbilirubinemia, 15 (4.68%) required phototherapy and none required exchange transfusion. TSB value of 4.40 mg/dl was estimated to be the best cut off value for risk prediction on day 1. Similarly 6.55 mg/dl was the best cut off value for day 2.

Conclusion: High TSB value at 24±4 & 48±4 hours successfully predicts significant hyperbilirubinemia subsequently. It also defines ideal cut-off values for Western Indian population. Babies with TSB values below 4.40 mg/dl at 24±4 hours & 6.55mg/dl at 48±4 hours can well be discharged early with no further follow up required sooner .

Key Words: Total serum bilirubin, Significant hyperbilirubinemia, Neonate, Prediction.

Introduction: Jaundice in newborn is quite common affecting ~70% of term and ~80% of preterm neonates of which only 5-25% is pathological [1-5]. National Neonatal Perinatal Database (NNPD) reported 6.1% incidence of significant hyperbilirubinemia in inborn neonates & 27.9% in outborns in the year 2002. But recent hospital based studies have shown a higher percentage nearing 25-35%. Neonatal brain is susceptible to toxicity from unconjugated bilirubin resulting in "kernicterus" [3,6] or bilirubin induced brain damage(BIBD).

The concept of early prediction of future risk for significant hyper-bilirubinemia is relevant because of the fact that it is the commonest cause for readmission to hospital after early discharge[1,7]. It is an important preventable form of mortality and morbidity even in low risk healthy babies[8,9]. Most such episodes occur > 72 hours of life. The current recommendations suggest follow up on day 2 & 3 of those babies discharged early[2,10]. But in any set up it is not always possible due to various geosocioeconomical and logistic reasons. Hence the predictivity of 24 & 48 hour TSB values in predating the future risk is of paramount importance [2].

The incidence of significant hyperbilirubinemia depends on ethnic make up, geography, laboratory methods, incidence of breast feeding, use of oxytocin like drugs, sibling history of jaundice & availability of quality obstetric facilities [5,8,11]. Many studies have mentioned that a larger prospective study is required before authenticating the results & cut-offs needed to be standardised to the heterogeneous Indian population [6,12].

The cut off values may also vary according to the geosocial factors, ethnicity, obstetric & child rearing practices in a given country & place[13]. The present study is an effort on the same lines in Western Indian population. The study aims at proving the predictive efficacy of 24 & 48 hour values & identifying optimal cut off TSB values.

Materials and Methods:

All healthy term/ near term newborns delivered at obstetric department, SSG Civil Hospital Vadodara, satisfying the criteria, willing to stay for 5 days as inpatient & for follow up if required later were selected and enrolled during 6 month period between Jan to June 2007. Informed consent was taken in each case.

Relevant details were collected in the standard proforma within the 24 hours. Maturity was scored accurately

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according to New Ballard's scoring system at the end of first day, correlated with EDD and antenatal USG reports. Detailed clinical examination was carried out to identify any neonates with exclusion criteria.

Routine investigations including blood/ Rh grouping, direct Coumb's test, peripheral smear & reticulocyte count and if required investigations like RBS, septic screen (at 12 and 48hours), G6PD assay, LFT, RFT etc were done. The samples were collected for TSB & PCV at 24, 48, 72, 96, 120 ±4hour. Any baby with TSB value falling in the therapeutic range was excluded further from study. TSB values were measured using Twin Beam Plus Bilirubinometer (Ginevri, CECCHINA, Italy), well calibrated (spectrophotometric method) & standardized with accuarcy of ±0.3mg/dl (<3%) which can read values up to a haematocrit of 80%[14]. Micro-capillaries of volume <70 micromoles used were of the same company to collect heal prick samples. Remi RM-12C micro centrifuge was used for centrifugation.

Any TSB value >10 mg% was confirmed with the 2 other laboratory reports & clinical assessment. PCV values were correlated as well. All such babies were sampled at more frequent intervals, followed up later on and additional tests were done as per indication. Feeding history was taken & each case was assessed thoroughly for lactation failure, colour of urine & stool & other relevant clinical details.

These neonates were daily being followed up from day 1 to 5 using heal prick blood samples collected & tested spectrophotometrically with bilirubinometer bedside. The TSB values were plotted using charts of Bhutani et al meant for discharge and follow up decision. Phototherapy was given according to the nomograms meant for the same.

The hour specific charts of Bhutani et al [15] were used to stratify the risk and was correlated it with clinical risk assessment by 2 independent clinical evaluators.

Definition : Primary outcome was significant hyperbilirubinemia defined as serum biliirubin value >15mg % in the first week of life in healthy term newborns (NNPD guidelines).

Inclusion:

1) Neonate >36 wks gestational maturity (New Ballard's scoring at 24hrs of life)

2) >2000 grams birthweight (Weighed using Electronic scale with ±10gm error)

3) On EBF and apparently healthy (daily clinical assessment)

4) Oxytocin usage is included as it is common to both cases and controls & its exclusion could not be accomplished.

Exclusion:

1. Birth asphyxia / hypoglycemia / acidosis/ trauma.
2. Received NICU care excluding observation.
3. Septicemia (EOS / LOS)
4. G6PD deficiency.
5. ABO/ Rh incompatibility /Coumb's positivity.
6. TSB values post intervention.
7. Any significant illness.
8. Gross congenital defects.

Study Design: Hospital based Prospective Cohort study.

Statistical Analysis:

The data was analysed at 95% confidence level with SPSS 15 to find out the critical TSB value at 24±4 and 48±4 hour respectively which predict the neonates at risk of developing significant hyperbilirubinemia subsequently using ROC curve. The specificity, sensitivity, positive & negative predictive values for the obtained cut-offs were calculated. Statistical analysis was done with descriptive analysis, independent sample t test & chi 2 tests.

Sample Size :

Keeping the confidence level of 95%, sample size of minimum 277 subjects was planned considering the annual rate of delivery at our hospital as ~4000per year and prevalence of significant hyperbilirubinemia as 7-10 %, with the design effect of 2. A risk of 5% was accepted for a desired precision of 5. To account for dropout (expected as ~10 %) we enrolled 344 infants.

Study Setting : Neonatal unit of department of pediatrics S.S.G.Hospital and Medical College, a tertiary care hospital Vadodara during the 6months from Jan 2007 to June 2007.

Results:

Of the total 567 eligible babies, 344 were enrolled in the study. Of them 24(6.9%) were excluded. Six babies developed sepsis, one developed hypoglycemia on day 2, one had congenital aqueduct stenosis and 16 failed to complete the study. Finally 320 babies completed the study. All infants were exclusively breastfed. The baseline characteristics of infants not enrolled were similar to those enrolled.

Table 1: questions determining knowledge about foot care

FACTORS	Total Babies N=320	Babies with TSB >15 mg/dlN=31
Male babies	159 (49.6%)	12 (38.7%)
Female babies	161 (50.3%)	12 (38.7%)
Birth weight 2000-2500 gm	145 (45.3%)	18 (58.06%)
2500-3000 gm	131 (40.9%)	05 (16.1%)
> 3000gm	44 (13.7%)	01 (3.2%)
AFD babies	293 (91.5%)	21 (67.7%)
SFD babies	20 (6.25%)	02 (6.45%)
LFD babies	07 (2.18%)	01 (3.2%)
PIH/ Eclampsia in mother	36 (11.3%)	04 (12.9%)
PROM >18 hrs	09 (2.8%)	01 (3.2%)
Oxytocin use	195 (60.1%)	12 (38.7%)
Multiple gestation	08 (2.5%)	01 (3.2%)
Drugs given to baby which may affect TSB level (includes vit-K)	154 (48.12%)	11 (35.48%)
History of jaundice in previous siblings	16 (5%)	09 (29%)
Feeding Problems/ Inadequate feeding	12 (3.8%)	06 (19.35%)
Borderline prematurity <37 week	7 (2.18%)	01 (3.2%)
Maternal age <20 yr	68 (21.3%)	11 (35.48%)
20-35yr	246 (76.9%)	19 (61.3%)
>35 yr	6 (1.8%)	1 (3.2%)
Parity 1	173 (54.1%)	13 (41.9%)
2	103 (32.1%)	7 (22.5%)
3	33 (10.3%)	7 (22.5%)
>3	11 (3.4%)	4 (12.9%)
Normal vaginally delivered	244 (76.25%)	24 (77.4%)
Cesarean section	62 (19.37%)	6 (19.35%)
Vaccum/ Forceps	14 (4.3%)	1 (3.2%)
Low SES (Class 3/ 4)	286 (89.4%)	26 (81.2%)
Mothers Uneducated	166 (51.8%)	18 (58.1%)
Antenatal care not taken	77 (24.1%)	18 (58.1%)
Blood Groups O	97 (30.3%)	10 (32.2%)
A	60 (18.7%)	6 (19.4%)
AB	95 (29.6%)	9 (29%)
B	68 (21.2%)	6 (19.4%)
PIH / Eclampsia	36 (11.3%)	7 (22.5%)
Oxytocin used	195 (60.1%)	18 (58%)
PROM >18 hrs	9 (2.8%)	2 (6.4%)
Gestational Diabetes	3 (0.94%)	1 (3.2%)
Ante partum bleeding	22 (6.8%)	2 (6.4%)

Table 2: shows the baseline characteristics of the population studied (maternal).

Total of 31 (9.6%) babies developed significant hyperbilirubinemia during the study period, 15 (4.68%) required phototherapy & none required exchange transfusion.

The study population was sub-divided .
Group 1: Babies developing significant hyperbilirubinemia (>15 mg %).
Group 2: Babies not developing significant hyperbilirubinemia (>15 mg %).

Since TSB estimation was done at 24±4 and 48±4 hour respectively for all subjects there is no statistically significant difference in the age at which the TSB was estimated.

Table 3: Analysis of age at the collection of samples for TSB estimation.

Group		Min	Max	Mean	S.D.	p-value
24±4 hours	Group 1:	21	28	24.4516	1.58826	0.982
	Group 2:	20	28	14.2990	1.75675	
48±4 hours	Group 1:	44	52	48.0645	1.69185	0.266
	Group 2:	44	52	48.0242	1.58205	

Table 4: Depicts very significant difference of 1st day TSB values between two groups.

Parameter	Group	Max	Mean	S.D.	p-value
TSB (mg/dl)	1	3.90	7.60	5.7710	0.000
	2	0.20	6.70	2.3768	

To determine the best cut-off value of 1st & 2nd day TSB value which would predict neonates likely to develop significant hyperbilirubinemia, ROC analysis was done.

Fig 1: ROC for selecting best cut-off value for risk prediction on day 1.

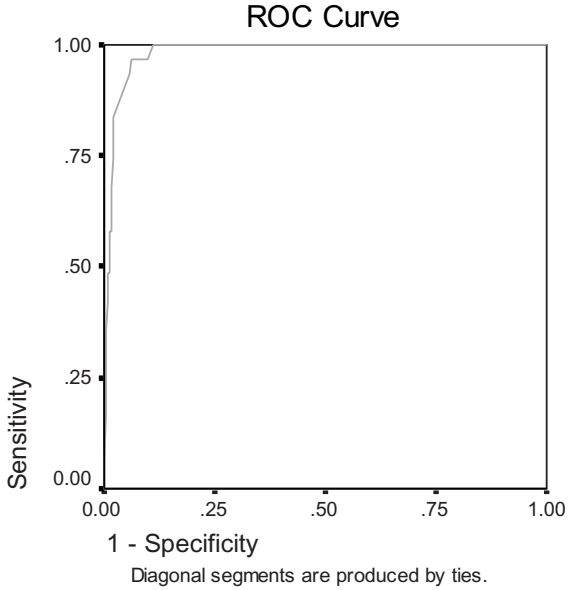
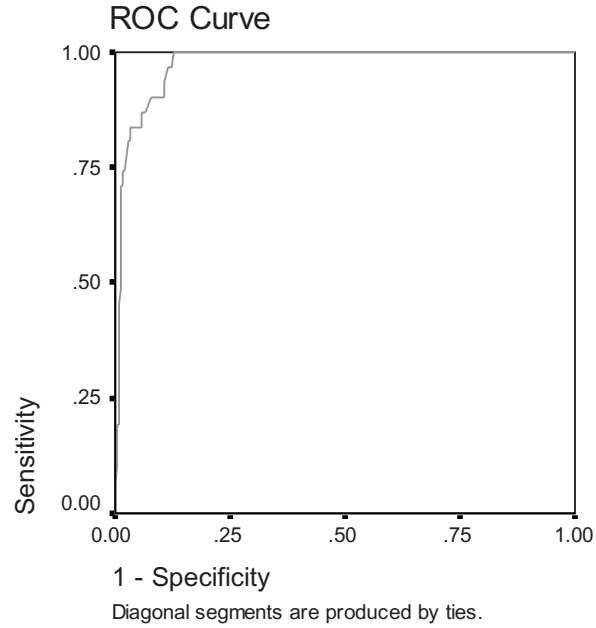


Table 5: Depicts the best predictive TSB values at 24±4 hours & 48±4 hours.

Parameter	TSB (mg/dl)	SN	SP	PPV	NPV
24±4 hours	e"4.40	96.8%	93.8%	62.5%	99.6%
48±4 hours	e"6.55	83.9%	94.5%	61.95	98.2%

Fig 2: ROC for selecting best cut-off value for risk prediction on day 2.



TSB value of 4.4 mg/dl was estimated to have best combination of high sensitivity, high specificity, low positive & high negative predictive values for risk prediction on day 1. Similarly 6.55 mg/dl on day 2 was found to be the critical value.

Discussion: The present study found that high TSB value at 24±4 & 48±4 hours successfully predicts the risk of significant hyperbilirubinemia subsequently. It also defines the ideal cut-off values for Western Indian population. Babies with TSB values below the cut-off value (4.4 mg/dl at 24±4 hours & 6.55mg/dl at 48±4 hours) can well be discharged early without the need for follow up immediately thus reducing the huge burden on

already limited resources[2]. This will go a long way in decreasing risk of BIBD. It may not be possible to do 24±4 hour value in all babies. Few patients may want discharge <18 hours or may come for follow up after day 1. Hence 48±4 hour value also becomes important.

V K Bhutani et al found in their prospective study of 1097 term & near term neonates by collecting samples daily at 24 hours interval from day 1 to 5 that no neonate with TSB value <5 mg/dl at 24±4 hours developed significant hyperbilirubinemia. However the study had only 25% of patients completing the follow up which is a major drawback. Later hour specific bilirubin nomograms were developed by V K Bhutani et al (11) in 1999 by large cohort study (2840 neonates followed serially for first 7 days of life). Infants at high risk zone (>95th %le) 18-72 hrs after birth have 40% risk of developing significant hyperbilirubinemia and those in low risk zone (<40th %le) have no risk (100%SN & 100% NPV) [16]. They found that of 6.1% of neonates with pre-discharge TSB >95th centile, 32.1% developed significant hyperbilirubinemia subsequently. But here the population is mostly top fed which is a very different from Indian population.

Alpay et al [17] in 2000 by a similar prospective study in Turkey concluded that use of 6mg/dl as critical value at 24 hours of life predicted nearly all term neonates (SN of 90% & NPV of 97.9%) with subsequent risk of significant hyperbilirubinemia (>17mg/dl) & will determine all those requiring phototherapy later on. Only 2.05% babies with 24 hour TSB < 6 mg/dl developed significant jaundice but none needed any treatment. Study did not include near term babies.

Similarly in study series including 1075 neonates Seidman et al found 5 mg/dl as a better cut off value for predicting significant hyperbilirubinemia with low sensitivity (45.5%), high specificity (91.9%) & high negative predictive value (99%) for risk prediction[16].

In 4 studies from 3 different countries the incidence of significant hyperbilirubinemia is reported to be between 1.7 to 12%. This is attributable to ethnic, geographic variants as well as local practices. Altitude is also supposed to be an independent risk factor for higher mean TSB values. Higher peak values mean a higher first & second day TSB values as well. Till recently there has been a paucity of such data from India [14].

A study from AIIMS, Delhi was done in term & near term neonates with ABO incompatible babies as controls. TSB value of > 5mg/dl was found to be the critical value at 24±6 hours for risk prediction. A study was conducted by A.K.Deorari & colleagues at AIIMS, Delhi, on 220 low risk term & near term neonates to evaluate the predictive efficacy of TSB >6mg/dl at 24±6 hours in detecting those who do not develop significant hyperbilirubinemia (>17mg/dl) subsequently[3]. The value >6mg/dl at first has proven to have high sensitivity (95%) and negative predictive value (93.5%)[15].They found that subsequent hyperbilirubinemia can be predicted with reasonable accuracy by plotting hour specific values on Bhutani's charts and correlating with clinical risk assessment. However sample size was small & larger Indian studies were needed before validation.

In another study from India, a TSB value >3.99mg/dl at 18-24 hour was found to predict the subsequent hyperbilirubinemia (>15mg/dl) with sensitivity and specificity of 67% [6]. Both studies opined that a large scale study would be needed before one could mean it as a recommendation/ protocol for Indian population [6,12].

Study done at IGMC, Shimla [14] on similar lines in 2003 (228 full term babies) concluded that 24±6 hour TSB value >6.4 mg/dl has the best combination of SN (87.5%), NPV (97.9%) & SP (80.1%). The incidence of hyperbilirubinemia was 12%. But higher mean TSB values may reflect the effect of high altitude & ethnic factor. But this relied heavily on clinical assessment which may be inaccurate.

There are certain drawbacks in our study as well. Though the sample is heterogeneous the effect of hospital stay for 5 days may be a source of bias since the feeding pattern of those at home & at hospital may different and may not reflect a real life situation. We did not follow up all patients beyond 5 days, some of who might have developed significant TSB values later on & not picked up. More studies especially large multicentric studies need to be done on Indian babies before the conclusions can be generalized.

Conclusion:

Present study found that high TSB values at 24±4 & 48±4 hours successfully predict significant hyperbilirubinemia subsequently. It also defines ideal cut-off values for Western Indian population. Babies with TSB values below 4.40 mg/dl at 24±4 hours & 6.55mg/dl at 48±4 hours can well be discharged early with no further follow up required sooner thus reducing the huge burden on already limited resources [12]. It may not be possible to do 24±4 hour value in all babies. Some patients may want discharge <18 hours or may come for follow up after day 1. Higher peak values mean a higher first & second day TSB values as well. Hence 48±4 hour TSB value is also important.

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