PREDICTION OF SIGNIFICANT NEONATAL HYPERBILIRUBINAEMIA IN HEALTHY TERM NEW BORNS USING 22-26 HOURS' SPECIFIC SERUM BILIRUBIN – A PROSPECTIVE STUDY

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ABSTRACT

INTRODUCTION

Hyperbilirubinemia invariably occurs in the newborns and is discerned as clinical jaundice in nearly 50% of infants. It is a cause of concern not only for the parents but also for the paediatricians. Bilirubin production is 2-3 times higher in normal term newborns compared with adults. The colour in jaundice usually results from accumulation of unconjugated, non-polar, lipid soluble, bilirubin pigment in the skin which is formed from haemoglobin by the action of heme oxygenase, biliverdin reductase and non-enzymatic reducing agents in the reticulo-endothelial cells.

AIMS & OBJECTIVE

To determine hour specific serum bilirubin (22-26 hrs) which will predict, subsequent significant hyperbilirubinemia in healthy term newborns.

MATERIALS & METHODS

A total of 250 healthy full term newborns were enrolled into the study. First bilirubin estimation (TSB 1) was estimated at 22-26 hrs. The neonates were followed up clinically every 12 hrs for 72 hrs (till discharge). Second bilirubin estimation (TSB S) was done whenever clinical suspicion of jaundice was present (usually at 72 hours). Depending upon the TSB 1 value, the infants were evaluated by using two available protocols (Arbitrary cut off value of 5 mg/dl and average value of 4.06 mg%). Sensitivity, specificity, negative and positive predictive values and likelihood ratio of the test were calculated. P-value was used to determine the level of significance.

RESULTS

Of 250 neonates included in the study, 13 neonates developed hyperbilirubinemia and were subjected to phototherapy. No infants with average bilirubin value of ≤4.06 mg% developed subsequent hyperbilirubinemia. However, 2 infants with arbitrary cut off value of ≤5 mg/dl developed hyperbilirubinemia. There was significant difference in TSB I value of neonates who subsequently did and those who did not developed significant hyperbilirubinemia (P-value-<0.01). The negative predictive value to these two applied protocol is very high (99.05% & 100%) indicating that infants with serum bilirubin level cuff off value of <5 mg/dl or average value of 4.06 mg% are at very low risk of developing subsequent significant hyperbilirubinemia.

CONCLUSION

The present study infers that total serum bilirubin level of less than 5.0 mg/dl or 4.06% at 22-26 hours of life predicts absence of subsequent hyperbilirubinemia with high probability and these infants can be discharged safely and early from the hospital. Neonates whose first bilirubin level is above the cut off value of 5.0 mg/dl or average value of 4.06 mg% are more prone to develop significant hyperbilirubinemia requiring phototherapy.

KEYWORDS

Hyperbilirubinemia, Neonate, Serum bilirubin, Phototherapy.

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INTRODUCTION: Hyperbilirubinemia invariably occurs in the newborns and is discerned as clinical jaundice in nearly 50% of infants. It is a cause of concern not only for the parents but also for the paediatricians. Bilirubin production is 2-3 times higher in normal term newborns compared with adults. The colour in jaundice usually results from accumulation of unconjugated, non-polar, lipid soluble, bilirubin pigment in the skin which is formed from

haemoglobin by the action of heme oxygenase, biliverdin reductase and non-enzymatic reducing agents in the reticulo-endothelial cells.

Under normal circumstances, the level of indirect reacting bilirubin in umbilical cord serum is 1-3 mg/dl and rises at the rate of less than 5 mg/dl/24 hrs. Thus jaundice becomes visible on the 2nd–3th day (36-72 hrs) usually peaking by the 3rd day at 5-6 mg/dl and decreasing to below 2 mg/dl between 5th and 7th day of life.[1]

Quantifying the level of jaundice has been the foundation for satisfactory management of hyperbilirubinemia. The observer variability and the influence of skin colour in clinically evaluating hyperbilirubinemia by Kramer's index[2] has been the Achilles heel of the method. Moreover, the current risk factors to recognize infants who are likely to require treatment for hyperbilirubinemia are not adequate.

While jaundice per se is not preventable nonetheless early detection of threatening bilirubin levels permit initiation of phototherapy and prevents higher risks and high cost exchange transfusion therapy or kernicterus. The AAP (American Academy of Pediatrics)[3] recommends that newborns discharged before or within 48 hours, should have follow-up visit after 2-3 days to detect significant jaundice and other problems. This is however not possible in our country due to limited follow up facilities.

The concept of prediction of jaundice offers an attractive option to pick up babies at risk for neonatal hyperbilirubinemia. An association between bilirubin levels and subsequent risk of hyperbilirubinemia has been reported.[4,5] Infants who are clinically jaundiced in the first few days are more likely to develop hyperbilirubinaemia.[6,7]

The golden standard for deciding therapy to prevent encephalopathy and kernicterus 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 bilirubin rises by "hours" of life and hence the time of sampling must be as 'hours of life' and not 'day of life'.[8] Hour specific percentile charts based on serum bilirubin at different ages have been developed. They show that subsequent hyperbilirubinemia can be predicted with reasonable accuracy by plotting for specific bilirubin on these charts.[9] There is paucity of literature on this concept of prediction of hyperbilirubinemia.

Hence, the present study was carried out to evaluate the predictive value of specific bilirubin level at 22 hours to 26 hours of postnatal age for identifying full term neonates at risk for subsequent hyperbilirubinemia.

METHODOLOGY: The present study is a hospital based prospective study which was carried out in the Postnatal care ward, Department of Pediatrics, Princess Esra Hospital, Hyderabad from May 2013 to June 2014. A total of 250 healthy, full term newborns (period of gestation 37-41 weeks, assessed by Expanded Ballard Score) weighing ≥2500 grams were included in the study. Serum bilirubin measurement was done by using monoreagent "Jendrassik and Grof" method. First bilirubin estimation (TSB 1) was done at 22-26 hrs. The neonates were followed up clinically every 12 hrs for 72 hrs (till discharge). Second bilirubin estimation (TSB S) was done whenever clinical suspicion of jaundice was present (usually at 72 hours). Phototherapy was started in babies who developed significant hyperbilirubinemia (TSB ≥ 15 mg/dl). Babies with significant neonatal illness requiring NICU admission >12 hours, Rh Incompatibility, major congenital malformations and conjugated hyperbilirubinemia were excluded from the study.

Depending upon the first bilirubin estimation (TSB 1) value, the newborns were classified into two groups using two available protocols.

Protocol I: Using cut off value of 5 mg/dl.[10]
Group 1: Serum bilirubin level more than 5 mg/dl.
Group 2: Serum bilirubin level less than 5 mg/dl.
Protocol II: Using average value of 4.06 mg%.[11]
Group 1: Neonates with bilirubin level more than 4.06 mg%.
Group 2: Neonates with bilirubin level less than 4.06 mg%.

Bilirubin Estimation: Serum bilirubin estimation was done using monoreagent "Jendrassik and Grof" method.[12,13] Whole blood was taken in micro-capillary and centrifuged at the rate of 300 rpm for 5 minutes. Bilirubin estimation was done spectrophotometrically using wavelength (530-560 nm) and bichromatic wavelength used was 540 nm. (Bil Micrometer–Semi Auto Analyzer, RA-50 Chemistry System).

STATISTICAL ANALYSIS: Maternal and neonatal data were collected in predesigned and pretested proforma. Sensitivity, specificity, negative and positive predictive values and likelihood ratio of the test were calculated. For determining significance of each test P-value was used.

RESULTS: A total of 250 healthy term newborn were evaluated. Their baseline data is given in table 1. All the newborns were exclusively breast fed starting within 2 hours of birth. At the end of the study, 13 newborns developed significant hyperbilirubinemia. No newborn developed Kernicterus or required exchanged transfusion.

Characteristics	Number (Percentage)
Maternal	
Type of delivery	
Full term normal vaginal delivery (FTND)	180 (72)
Cesarean	62 (24.8)
Instrumentation	08 (3.2)
Parity	
1	95 (38)
2	81 (32.4)
3	44 (17.6)
>4	30 (12)
Oxytocin use	100 (40)
Rupture of membranes (=18hrs)	19 (17.6)
Bad obstetric history	15 (6)
Pregnancy induced hypertension	9 (3.6)
Blood Group	
A	78 (31.2)
B	87 (34.8)
AB	17 (6.8)
O	68 (27.2)
Neonatal	
Male	122 (48.8)
Female	128 (51.2)
Period of Gestation (Mean)	38±1.4 (range 37-42)
Birth weight (in gm)(Mean)	2950±430 (range 2500-3800)
History of icterus in previous siblings	5 (2)

Table 1: Base line characteristics of enrolled newborns

The study population was divided into two subgroups based on first Total serum bilirubin (TSB 1) value using two available protocols. Distribution of new borns based on these protocols is given in figure 1 & 2. A majority of neonates had their arbitrary cut-off value of serum bilirubin level ≤5 mg/dl (84.4%) or average bilirubin value of ≤4.06% (55.2%)

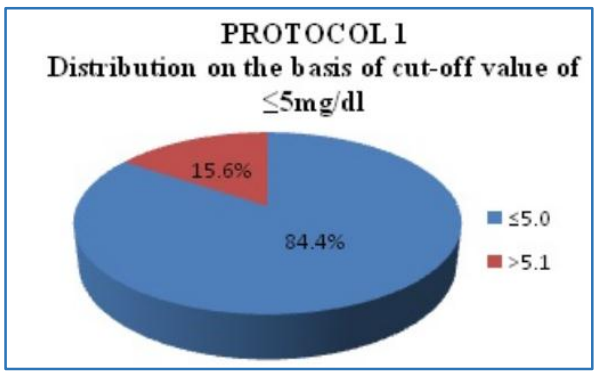

Fig. 1

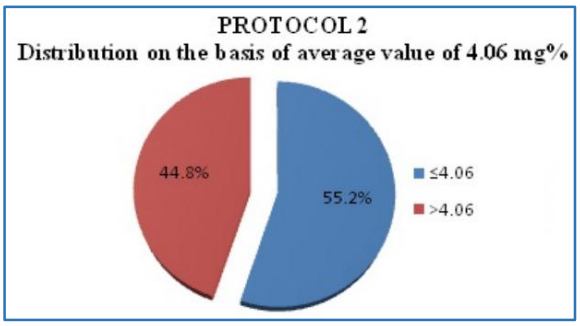

Fig. 2

Thirteen new borns that developed subsequent significant hyperbilirubinemia were subjected to phototherapy. A detailed characteristic of newborns that developed significant hyperbilirubinemia is given in table 2. No infant having average bilirubin value of ≤4.06 mg% developed subsequent hyperbilirubinemia. However, 2 infants having arbitrary cut off value of ≤5 mg/dl developed hyperbilirubinemia (table 3 & 4). These two protocols have high specificity and sensitivity. The predictive ability of these protocols is given in table 5.

Sl. No.	High risk factor	BG of mother	Type of delivery	Birth wt.(Kg)	Sex	Gestation (weeks)	TSB 1 24±2 hrs (mg/dl)	TSBS 72 hrs (mg/dl)	Duration of photo therapy (hrs)
1.	Anaemia	B+	FTND	3.1	M	39	5.0	17.6	18
2.	None	O+	LSCS	2.7	F	37	7.2	17.2	22
3.	PROM	A+	LSCS	2.6	F	40	6.7	16.9	10
4.	None	A+	FTND	3.3	M	38	5.5	16.2	16
5.	None	O+	FTND	2.7	M	37	6.5	18.2	46
6.	BOH	O+	LSCS	2.9	F	39	6.0	18.4	48
7.	None	AB+	FTND	2.5	M	37	8.8	17.5	30
8.	None	B+	FTND	2.8	F	38	6.8	16.9	14
9.	PIH	O+	LSCS	3.2	F	39	8.7	19.3	54
10.	PROM	B+	Forceps	2.9	M	39	8.8	19.0	48
11.	None	O+	LSCS	3.3	M	40	6.8	17.0	12
12.	PROM	A+	LSCS	2.6	M	38	5.0	16.2	18
13.	None	O+	FTND	2.6	F	38	5.3	18.1	44

Table 2: Characteristics of newborns that developed significant Hyperbilirubinemia

TSB 1 (22-26 hrs) mg/dl	Number of newborns	Frequency of newborns with significant Hyperbilirubinemia
≤5.0	211	2
>5.1	39	11
Total	**250**	**13**

Table 3: Distribution of 13 Newborns with Significant Hyperbilirubinemia into 2 groups on the arbitrary cut off value of 5 mg%

Average Bilirubin value (mg/dl)	Number of newborns	Frequency of newborns with significant Hyperbilirubinemia
≤4.06	138	--
>4.06	112	13
Total	**250**	**13**

Table 4: Distribution of 13 Newborns with Significant Hyperbilirubinemia into 2 groups on the basis of Average Bilirubin value of ≤4.06

TSB 1	Specificity	Sensitivity	PPV	NPV	P-value
Protocol 1 (>5.0 mg/dl)	88.1 8%	84.62%	28.20 %	99.05%	<0.01 [Z=3.74] Highly significant
Protocol 2 (>4.06 mg%)	58.23%	100%	11.61 %	100%	<0.01 [Z=3.83] Highly Significant

Table 5: Predictive ability of Arbitrary cut off value of ≤5 mg/dl and Average Bilirubin value of ≤4.06

DISCUSSION: Our study hypothesis was that a high serum bilirubin level soon after birth i.e., 24±2 hours, would predict a high peak later in life. We considered peak serum bilirubin level ≥15 mg/dl as "Hyperbilirubinemia" as specific treatment is generally considered at or above this level. In the present study, the incidence of hyperbilirubinemia was 5.2% which was less than that observed in other studies.[12]

Of the total 250 newborns enrolled, 51.2% babies were females and 48.8% were males. It was observed that peak serum bilirubin levels were higher in neonates born after oxytocin induction of labour and delivery by Caesarean section and similar findings have been reported by others.[14,15] Of the 13 newborns who eventually developed hyperbilirubinemia at least 6 mothers of the infants had risk factors viz., anaemia, bad obstetric history and pregnancy induced hypertension, all of which have been associated with high serum bilirubin levels in the first postnatal week.[16,17] All newborns in our study were exclusively breast fed and feeding was initiated within first 2 hours of birth which was not found to be associated with peak serum bilirubin of the first 3 days. Similar findings were also reported in the study done by Awasthi et al.[13]

The obtained serum bilirubin values were evaluated by using two available protocols i.e., Protocol I (by using arbitrary cut off value of ≤5.0 mg/dl) and Protocol II (on the basis of average Bilirubin value of 4.06 mg%). Out of 39 newborns that had their first bilirubin level more than ≤5mg/dl, 11 developed significant hyperbilirubinemia requiring phototherapy. Thus, it could predict subsequent hyperbilirubinemia with sensitivity of 86.42% and specificity of 88.18%. A study conducted by Alpay et al[17] reported that TSB level >6.0 mg/dl in the first 24 hours of life will predict nearly all the full term newborns who will have significant hyperbilirubinemia. This critical bilirubin cut off value of 6.0 mg/dl although had a good sensitivity (90%) but had a reasonable negative predictive value (97.9%). Another similar study conducted by Agarwal et al[12] concluded that ideal cut off was 5.0 mg/dl and babies with TSB levels higher than 6.0 mg/dl had a significant risk of developing hyperbilirubinemia.

When newborns were divided in two groups using average value of 4.06 mg%, no newborn less than 4.06 mg% developed significant hyperbilirubinemia. Out of 112 newborns that had their bilirubin value more than 4.06 mg% 13 developed significant hyperbilirubinemia requiring phototherapy. Thus the average value can predict subsequent hyperbilirubinemia with specificity of 58.23% and sensitivity of 100%. In the study done by Awasthi S et al,[13] a value of 3.99 mg/dl (average value of first day TSB) was used to predict occurrence of subsequent hyperbilirubinemia. The sensitivity and specificity of this test was 67%. However, this study had major flaws. Complete follow up was conducted in neonates who stayed in the hospital for either neonatal illness or maternal reasons. More than 50% of newborns, who were healthy were discharged early not followed up.

By implying a significant difference in 24±2 hours' specific serum bilirubin values of newborns who subsequently did and those who did not develop significant hyperbilirubinemia, the present study had showed that hours specific (22 to 26 hours) bilirubin can definitely predict the incidence of subsequent hyperbilirubinemia in healthy term newborns. The negative predictive value to these two applied protocol is very high (99.05% & 100%) indicating that infants with serum bilirubin level cuff off value of <5 mg/dl or average value of 4.06 mg% are at very low risk of developing subsequent significant hyperbilirubinemia.

LIMITATIONS: The newborns were only assessed clinically for progression of jaundice and clinical evaluation might not be regarded reliable by some researchers. The newborns were followed up to the 3rd day of life and it is likely that few of the babies could have experienced late jaundice and may have been missed.

CONCLUSION: The present study highlights that total serum bilirubin level of less than 5.0 mg/dl or 4.06% at 22-26 hours of life predicts absence of subsequent hyperbilirubinemia with high probability and these infants can be discharged safely and early from the hospital. Term neonates whose first bilirubin level is above the cut off value of 5.0 mg/dl or average value of 4.06 mg% are more prone to develop significant hyperbilirubinemia requiring phototherapy. Prediction of neonatal hyperbilirubinemia has wide spread implications especially in our country where early discharge is a norm due to fewer hospitals beds, limited health care professional, very large patient and economic constraints. Hence, guidelines or policies against early discharges may not be practical. A more effective and careful approach focusing on neonates who are at risk of developing significant hyperbilirubinemia may be appropriate for further intervention or follow-up.

ABBREVIATIONS:

AAP: American Academy of Pediatrics.
BOH: Bad Obstetric History.
FTND: Full term Normal Delivery.
LSCS: Lower Segment Caesarean Section.
NICU: Neonatal Intensive Care Unit.
NPV: Negative Predictive Value.
PIH: Pregnancy Induced Hypertension.
PPV: Positive Predictive Value.
PROM: Premature Rupture of Membrane.
TSB 1: Total Serum Bilirubin at 22-26 hours.
TSB S: Total Serum Bilirubin at 72 hours.

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