

Approach to Hyperbilirubinemia in Near Term Infants

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ABSTRACT

Introduction: Hyperbilirubinemia is one of the most common clinical sign encountered in newborns which if untreated is potentially neurotoxic. There is a need for early prediction of jaundice to spot those babies at risk and intervene. Study aimed to determine the predictive value of cord and serum bilirubin 24 hours after birth to identify near term new born babies at risk of developing significant hyperbilirubinemia and identify the other clinical risk factors for significant hyperbilirubinemia which would determine their predictive values.

Material and methods: A cross sectional prospective hospital based follow up study involving consecutive near term neonates. We have studied 180 healthy term neonates, over a period of 5 month, with mean birth weight ranging from 2.0 to 2.5 kg. The cord and 24 hour bilirubin was measured in all babies and 5th day bilirubin measured in only jaundice babies.

Results: Incidence of significant jaundice in our study was 12.2%. The difference of mean cord and 24 hours serum bilirubin in jaundiced and Non jaundiced babies was statistically extremely significant [P<0.001] There was an excellent correlation between mean values of cord bilirubin, 24th hour TSB and day 5 TSB (p < 0.001). Mean cord and 24th hour TSB Level were high in male babies, babies born by SVD, babies born to multigravida mother, to mother with antenatal complications, babies with h/o jaundice in sibling, with cephalhematoma, with mother received oxytocin, maternal blood group 'O' and babies with Non 'O' blood group.

Conclusion: Our results indicate that 24th hour TSB \leq 6.2 mg/dl will predict babies who are unlikely to develop significant hyperbilirubinemia subsequently. Use of cord bilirubin value, 24th hour serum bilirubin value and clinical risk factor will be of benefit in our country with limited resources and follow up facilities.

Keywords: Hyperbilirubinemia, near term infants, cord bilirubin

INTRODUCTION

Hyperbilirubinemia is one of the most common clinical sign encountered in newborns and in most cases a benign problem. If untreated, severe unconjugated hyperbilirubinemia is potentially neurotoxic.¹ Neonatal jaundice is seen in two thirds of entirely healthy term newborn¹ and in a greater proportion of preterm's (80%),¹ in the first week of life. The non physiological or pathological hyperbilirubinemia in 5-10% of healthy term newborn^{1,2} is the most common reason for readmission of neonates in the first week of life in the current era of early postnatal discharge from the hospital.³⁻⁵

6.1% of term newborn, who were otherwise normal have a maximal serum bilirubin over 12.9 mg/dl⁵ and it is an alarming fact that serum bilirubin level were over 15 mg/dl found in 3% of healthy babies. Role of bilirubin in newborn has been an enigma because of its dual role as a potent natural antioxidant and at the same time having a cytotoxic effect for producing bilirubin induced neurological dysfunction. As there is no cut off value of bilirubin level that can cause bilirubin encephalopathy, neonatal jaundice has become a serious cause of concern for both

parents and pediatrician as well.¹ Thus every jaundiced baby necessitates attention at the earliest to look for the feature of pathological jaundice. After the reports of kernicterus occurring in healthy newborns even without hemolysis, have come to the forefront, there has been an increased apprehension with regard to Jaundice.⁶

In a cohort of 500 healthy term neonates, Alpay et al found that hyperbilirubinemia has occurred only after 72 hours of age.⁷ Also American academy of Pediatrics recommends that neonates discharged within 48 hours should have a follow up visit after 2-3 days to detect significant jaundice and other problems.⁸ However, this is a difficult proposition as many babies discharged early may not come for a review. Hence, the concept of early prediction of jaundice offers an attractive option to spot those babies at risk and intervene.

The dire need for early prediction of significant jaundice and the paucity of such studies from India acted as an impetus to undertake the present study- "hyperbilirubinemia in nearterm infants". This study could make a significant contribution to the neonatal care especially it being the first of its kind in South India, and one of the few studies undertaken in India. Study was aimed to determine the predictive value of cord bilirubin and serum bilirubin 24 hours after birth to identify near term new born babies at risk of developing significant hyperbilirubinemia and to identify the other clinical risk factors for significant hyperbilirubinemia that would determine their predictive values.

MATERIAL AND METHODS

A cross sectional prospective hospital based follow up study involving consecutive near term neonates over 5 months was done after taking the hospital ethics committee approval and informed patients consent.

Inclusion criteria

1. Near term newborn babies born at Shadan Hospital a tertiary Hospital "from 34- 37 weeks of gestation.
2. Babies weighing from 2.0 to 2.5 kgs

Exclusion criteria

1. Babies requiring admission to NICU for various neonatal complications.
2. Infants of diabetic mother
3. Neonates with major congenital malformations
4. Newborn babies born to HIV positive and HBs Ag positive mothers
5. Newborn born to RH - mother

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A total of 180 babies were enrolled in to study based on inclusion exclusion criteria. Gestational age of each baby was attested with the aid of LMP, EDD and antenatal ultra sound dating and it was confirmed by using new Ballard's score. Cord blood was collected soon after the delivery and analyzed by spectrophotometer model number 106 by spectral method. For all 180 babies blood sampling was done at 24 hours +/- six hours post natal age for estimation of total serum bilirubin (TSB) levels. TSB levels were estimated by spectrophotometry by spectral method. The effect of haemolysis was eliminated by subtracting the 450 nm absorbance from 454 nm and thus only bilirubin absorbance is measured. This is suitable for neonates less than 2-3 weeks only. All babies were followed on day 5 for the evidence of neonatal jaundice. Day 5 serum bilirubin was estimated for those icteric babies, who had yellowish discoloration extending below the knees. Babies with icterus up to the palms and soles with TSB < 15 mg/dl were kept under photo therapy and exchanged transfusion was done as per guidelines. Babies with significant jaundice on day 5 were further investigated with hemoglobin percentage, peripheral blood smear, reticulocyte count and direct coombs test.

STATISTICAL ANALYSIS

Statistical test like ANOVA, Mann-Whitney U test along with descriptive statistics were used to infer results. All the analysis was done with the help of SPSS version 21.

RESULTS

Demographic parameters of all the babies

Our study included 180 newborn babies, born at near term gestation, weighting from 2.0 to 2.5 kg, with mean birth weight. The sex ratio was Male: Female = 51.7%/48.3% (n=93/87) = 1.07: 1. The demographic parameter of jaundiced babies showed that out of 180 babies 22 babies developed significant jaundice on day 5 (Incidents 12.20%). The mean birth weight of these jaundiced babies was ranging from 2.0 - 2.5 kg. The mean times of 24th hours TSB estimation was 25.56 hours +/- 1.539 hours ranging from 22 to 30 hours and mean 24 hours TSB levels were 6.89 mg/dl +/- 1.25 mg/dl ranging from 4 to 9 mg/dl. The mean day 5 TSB level were 16.9 mg/dl +/- 1.61 mg/dl ranging from 13 to 19 mg/dl. There was no co relation between 24th hour TSB and day 5 TSB, $r = -0.199$ and $p = 0.375$.

Distribution of jaundiced babies according to sex

Male to female sex ratio among jaundiced baby was 2.6:1 (16/6). Males were 2.6 times more than female among jaundice babies. There is an association between male sex and presence of jaundice with $\chi^2 = 4.46$ and $P = 0.035$ which is statistically significant.

Distribution of jaundiced babies according to mode of delivery

Babies born by SVD had higher incidents of neonatal jaundice. Of the jaundiced babies 12 had SVD, 4 LSCS, and 6 EmLSCS. All 100% of babies received vitamin K (n=22).

Distribution of jaundiced babies according to cephalhematoma

50% of jaundice newborns had cephalhematoma (n=11). An association was present between presence of cephalhematoma and presence of jaundice with $P > 0.01$, which is statistically significant.

Distribution of jaundice according to parity

Of the jaundiced babies 15 were born to multigravida and 7 to primigravida.

Distribution of jaundiced babies according to antenatal complications

More numbers of babies with jaundice were born to mothers having PROM > 12Hours (n=6) PIH in 3 and 13 had nil complications. PIH was there in 53 of the non jaundiced and none of latter had PROM.

Comparison of demographic parameters in babies with and without jaundice (table 1)

And higher number of jaundiced babies were born by NVD, Multigravida mother and mother who has received L.A but it was not statistically significant.

Among the jaundiced babies mean Hb % was 13 gm% ranging from 12 gm% to 14 gm%, mean reticulocyte count was 3% ranging from 2-4 %. out of 22 babies DCT was done in all babies and no babies had positive DCT.

Comparison of mothers and babies blood groups among jaundiced and non-jaundiced babies

Babies (n=19) (86.4%) with jaundice where born to mother with O blood group and ABO incompatibility was present in n=12 (63.2%) babies.

OA incompatibility was present in n=2 (10.5%) babies and OB incompatibility was present in n=10 (52.6%) of babies. Rest of the babies didn't have any incompatibility and had various combination of blood group. When number is < 5 in the cell then "Fisher's Exact Test" was done.

Mother with O blood group and babies with Non O blood group has P value of <0.05 which is statistically significant and baby is at high risk of developing significant jaundice.

Mean 24th hour tsb and cord tsb among jaundiced and non jaundiced

Among Jaundiced babies (n=22), the mean cord TSB = 2.1 mg/dl, with a SD = +/- 0.06 mg/dl and mean 24th hour TSB = 6.9 mg/dl, SD = +/- 0.27 mg/dl. Among Non Jaundiced babies (n=158) the mean cord TSB = 1.3 mg/dl, SD = +/- 0.02 mg/dl and mean 24th hour TSB = 4.7 mg/dl, SD = +/- 0.04 mg/dl. The mean cord TSB and mean 24th Hour TSB was high in jaundiced babies compared to Non-Jaundiced babies.

Correlation between the mean 24th hour TSB levels and clinical risk factors

Mean 24th hour TSB levels vs sex of the newborn: Mean 24th hour TSB levels were high in male babies compared to female babies but it is statistically not significant.

Mean 24th hour TSB levels vs gravid mean 24th hours TSB levels were high in babies born to Multigravida mother and the difference was statistically significant by non parametric mann-whitney test.

Mean 24th hour TSB vs jaundice in sibling: Mean 24th hour TSB levels were high in babies with history of jaundice in sibling and it was statistically significant with $p < 0.001$ in jaundice babies (n=16) it was 6.70(SD 1.40) and in non jaundice (n=164) it was 4.80(SD0.70)

Mean 24th hour TSB levels vs cephalhematoma: Mean 24th hour TSB levels in jaundice (n=18) was 6.1(SD 1.53) and in non jaundice babies (n=162) it was 4.9(SD 0.77).

Sr no.	Parameter	Jaundiced n=22	Non Jaundiced n=158	P Value
1.	Sex	Male=72.7% (n=16) Female=27.3% (n=6)	Male=48.7% (n=77) Female=51.3% (n=81)	<0.05
2.	Mean birth weight	2.89 kgs+/- 0.213 kgs	2.85 kgs +/- 0.80 kgs	
3.	Mode of delivery			NS
	SVD	n=12 (54.5%)	n=72 (45.6%)	
	LSCS	n=4 (18.2%)	n=63 (39.9%)	
	EmLSCS	n=6 (27.3%)	n=20 (12.7%)	
	Forcep	n=0 (0%)	n=3 (1.9%)	
4.	Gravida			0.25 (NS)
	Primi	n=7 (31.8%)	n=73 (46.2%)	
	Multi	n=15 (68.2%)	n=85 (53.8%)	
5.	Anenatal complication			<0.0001 (S)
	PIH	n=3 (13.6%)	n=53 (33.5%)	
	PROM	n=6 (27.3%)	n=0 (0%)	
	NONE	n=13 (59.1%)	n=105 (66.5%)	
6.	Jaundice in sibling	n=12 (54.5%)	n=4 (2.5 %)	----
7.	Vit -k	n=22 (100%)	n=158 (100%)	<0.001 (S)
8.	Cephalhemato-ma	n=11(50%)	n= 7(4.4%)	

Table-1: Comparison of Demographic parameters in babies with and without jaundice

Mean 24th hour TSB levels were high in babies having Cephalhematoma and it was statistically significant.

Mean 24th hour TSB levels vs mothers blood group: The Mean 24th hour TSB levels in babies born to mother having 'O' blood group (n=97) was 5.30(SD 1.05) and in non "O" group was 4.60(SD 0.63). Mean 24th hour TSB levels were high in babies born to mother having 'O' blood group which was statistically significant (p<0.001)

Mean 24th hour TSB vs baby blood group: The Mean 24th hour TSB levels in babies with 'O' blood group (n=78) was 5.00(SD 0.61) and in Non "O" group (n=102) was 4.98 (SD 1.13). Mean 24th hour TSB levels were high in babies with 'O' blood group but it was not statistically significant (0.77)

All babies with mother having 'O' blood group compared with baby's blood group

Babies with 'O' group (n=78) had mean 24th hour TSB (mg/dl) of 5.10 (SD 0.61) and in Non 'O' group (n=19) it was 6.60 (SD 1.51) and was statistically significant (p<0.001). So mother with 'O' blood group and baby with Non 'O' blood group has higher mean 24th hour TSB value which was statistically significant and such babies are at high risk of developing significant jaundice. So mean 24th hour TSB levels were high in babies born to Multi gravid mother, babies with history of jaundice in sibling, babies with cephalhematoma, babies with mother having 'O' blood group and babies with Non 'O' blood group; which was statistically significant.

And mean 24th hour TSB levels were high in Male child, Babies born by SVD and mother who has received Oxytocin but it was statistically not significant.

Mean cord bilirubin vs sex of the newborn

Mean cord bilirubin levels in male babies (n=93) was 1.50 (SD 0.37) and in female babies (n=87) was 1.30(SD 0.40) which was statistically significant. Mean cord bilirubin levels were high in male babies which is statistically significant (<0.001).

Mean cord bilirubin levels vs mode of delivery.

Mean cord bilirubin levels in babies born by SVD (n=84) was 1.50 (SD 0.38) and Em.LSCS (n=26) was 1.70 (SD0.29) Mean cord bilirubin levels were high in babies born by SVD and

Em.LSCS which was statistically significant (p<0.001)

Mean cord bilirubin levels vs gravid

Mean cord bilirubin levels in babies delivered by Multi gravida mother (n=100) was 1.44(SD 0.430) and in Primi (n=80) was 1.38(SD 0.345). Mean cord bilirubin levels were high in babies delivered by Multi gravida mother but it was statistically not significant.

Mean cord bilirubin levels were high in babies with mother having PROM>12 hour and it was statistically significant. These could be explained by increased perinatal stress in these babies (Table 2).

Mean cord bilirubin levels vs jaundice in sibling

Mean cord bilirubin levels in babies with history of jaundice in sibling (n= 16) was 1.94(SD 0.408) and in non jaundice babies (n=164) was 1.36 (SD 0.355). Mean cord bilirubin levels were high in babies with history of jaundice in sibling and it was statistically significant (p<0.001).

Mean cord bilirubin levels vs baby blood group

Mean cord bilirubin levels were high in babies with Non 'O' blood group but it was statistically not significant (0.171).

All babies with mother having 'O' blood group are compared with baby blood group

Mean cord bilirubin levels in babies having Non 'O' blood group (n=19) was 1.87(SD0.417) and in 'O' group (n=78) was 1.37(SD0.379). Mean cord bilirubin levels were high in babies having Non 'O' blood group and mother having 'O' blood group which was statistically significant (p<0.001) So mean cord bilirubin values were high in Male babies, babies delivered by NVD and Em. LSCS, babies with mother having PROM>12 hours, babies with H/O jaundice in sibling, babies whose mother has received intrapartum Oxytocin, babies with mother having 'O' blood group and baby having Non 'O' blood group and it was statistically significant. And mean cord bilirubin values were high in babies delivered by multi gravida mother but it was statistically not significant.

Since samples were tested at 3 different time points (at birth, at 24th hour and at 5th day) repeated measures of ANOVA was

performed to know whether there exist any significant difference between the mean values of bilirubin (Table 3).

DISCUSSION

Early discharges of the near term newborns from the hospital after delivery has recently become a common practice for medical, social, and economic reasons. However it has shown that newborns whose post delivery hospital stay is ≤ 72 hours are at a significantly greater risk of readmission then those whose stay is > 72 hours.^{4,7,23} Hyperbilirubinemia is the most commonly reported cause for the readmission during early neonatal period,^{4,7,11,10} and 0.36% of healthy term newborns discharged after 72 hours of life with mild hyperbilirubinemia may even develop subsequent moderate to severe hyperbilirubinemia.¹¹ In United States there were 22 reported cases of kernicterus developing in babies discharged within 48 hours after birth.¹⁶⁻²⁰ Furthermore the safety of relying on follow up visits after early discharge is questionable as 10 % of the population fails to return for a follow up visit.^{12,13}

Hence it is crucial to categorize the babies who are at risk for significant jaundice to prevent the potential bilirubin neurotoxicity. The desperate need for early prediction of significant jaundice and paucity of such studies from India has spurred us to undertake this prospective follow up study.

Studies available from the west and north India have used either cord bilirubin or 24th hour total serum bilirubin for prediction of significant hyperbilirubinemia (Table-4). We have designed this study to determine the predictive values of cord bilirubin, 24th hour serum bilirubin and clinical risk factors to identify the newborns at risk of significant hyperbilirubinemia.

Incident of Jaundice: We have found the incident of significant jaundice to be around 12.2 % which was comparable with other studies from India.¹⁴⁻¹⁶ and USA.¹ We have studied the impact of

ANC	N	Mean cord TSB (mg/dl)	SD	P value.
PIH	56	1.32	0.343	0.001
PROM>12hr	6	2.08	0.264	
Nil	118	1.42	0.393	
Total	180	1.41	0.40	

Table-2: Mean cord bilirubin levels vs antenatal complications.

Time Point	Mean	SD	P Value
Cord bilirubin	2.10	0.28	<0.001 (S)
24 th hour bilirubin	6.90	1.25	
5 th day bilirubin	16.90	1.61	

So there is a significant difference between all 3 mean values at 3 different time points with $P < 0.001$ [n=22], which is statistically significant.

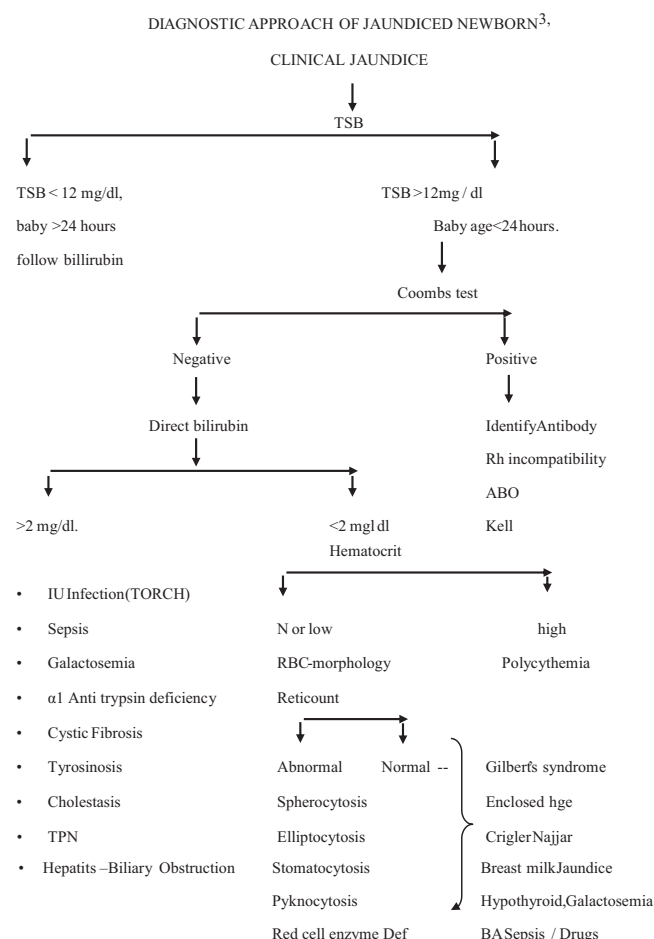
Table-3: Mean values of bilirubin at 3 different time points

Name of study	No. Of babies	Def. Of significant Jaundice	Time of sampling on Day-1	24 th hour TSB cut off	Sensitivity	Specificity	PPV	NPV
Our study	180	TSB>15 mg/dl	24+/- 6 hours	≥ 6.2 mg/dl	94%	96.4%	92.3%	99.25%
Alpay etal ⁷	498	TSB>17 mg/dl	24 hours	≥ 6 mg/dl	90%	-	-	97.9%
Avasthi etal ²²	274	TSB>15 mg/dl	18-24 hours	> 3.99 mg/dl	67%	67%	-	-
Aggrawal etal ²³	220	TSB>17 mg/dl	24+/- 6 hours	< 6 mg/dl	95%	70.6%	27.7%	99.3%

Table-4: Comparison of our study with previous studies

barriers epidemiological factors over the incidents of significant jaundice. Males were 2.6% more jaundiced than females in our studies. Similar association was demonstrated by Friedman et al, Maisels et al and Anand et al.^{16,15}

Our study has shown that male sex, spontaneous vaginal delivery (due to increased perinatal stress) multigravida, oxytocin induction, cephalhematoma, history of jaundice in the sibling were associated with increased incident of jaundice. Also we could demonstrate the statistically significant association between male sex, spontaneous vaginal delivery, history of jaundice in sibling, cephalhematoma, use of oxytocin, history of PROM in mother, mother with "O" blood group and baby with non "O" blood group has significant jaundice. Khoury et al demonstrated the impact of jaundice in sibling over the present child. He has shown that present child has three times more risk of jaundice if the previous child had TSB > 12 mg/dl and the risk is 12.5 times if the sibling had TSB more than 15 mg/dl We have found that 63.2% (n=12) of the jaundiced babies had ABO incompatibility out of which 10.5% (n=2) had OA incompatibility and 52.6% (n=10) had OB incompatibility. In



western studies OA incompatibility is more common than OB incompatibility. As “B” blood group is second most common blood group in India after “O” blood group we can explain the higher incident of OB incompatibility in our set up.

Our study aimed to predict significant hyperbilirubimemia using Cord bilirubin and 24 hour serum bilirubin. We have co related these values with clinical risk factors. We have established that cord bilirubin cut off value ≥ 1.95 mg/dl and 24th hour total serum bilirubin cut off value ≥ 6.2 mg/dl has good predictive value for identifying newborns at risk of jaundice with:

Area under curve = 95.00%, Sensitivity = 94.00%, Specificity = 96.40%, Positive predictive value = 92.30%, Negative predictive value = 99.25%, False positive rate = 1.50% and P value < 0.0001 .

Rosenfeld et al¹⁶ uses cord bilirubin > 2 mg/dl for predicting significant hyperbilirubimemia. Also Knudsen et al found that cord bilirubin level > 2.3 mg/dl was associated with increased risk of jaundice¹⁷

Our study confirmed that mean cord bilirubin levels and 24th hour TSB Level were higher in male babies, babies born by SVD, babies born to multigravida mother, babies born to mother with antenatal complications, babies with H/O jaundice in sibling, babies with cephalhematoma, babies with mother who has received oxytocin, maternal blood group ‘O’ and babies with Non ‘O’ blood group, and these were statistically significant. Indicating a good correlation between cord bilirubin, 24th hour TSB and clinical risk factor.

There was an excellent correlation between mean values of cord bilirubin, 24th hour TSB and day 5 TSB with $p < 0.001$ which is statistically highly significant [Repeated measures of ANOVA] (Table 3).

To summarize we have shown that it is possible to predict significant hyperbilirubinemia using cord bilirubin, 24th hour serum bilirubin and clinical risk factor.

Limitations of our study

Total serum bilirubin level estimation was not done in all babies on day 5 as they were not having clinically significant jaundice and it was though unethical to collect a sample from such babies. We followed babies only up to day 5, so some of the late causes of jaundice might have been missed and they are likely to be very small in number and it is not of a real concern

CONCLUSION

our results indicate that 24th hour TSB ≤ 6.2 mg/dl will predict babies who are unlikely to develop significant hyperbilirubinemia subsequently. Use of cord bilirubin value, 24th hour serum bilirubin value and clinical risk factor will be of benefit in our country with limited resources and follow up facilities. Infant at low risk for hyperbilirubinemia can be discharged early at 24 hours of life.

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