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First Day (24±2hr) Serum Bilirubin Level, as Predictor of Significant Hyperbilirubinemia in Neonates

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Research Article

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Abstract

Background: Age-specific (24±2hours) predictive value of total Serum Bilirubin (TSB) ≤ 6 mg/dl in developing significant hyperbilirubinemia in infants

Methods: A Prospective observational study on 200 term neonates having birth weight ≥2500 gm and gestational age ≥37 weeks. Blood was collected from the venous site. The blood samples of all infants were sent for grouping and TSB estimation. Babies were clinically examined every day for jaundice. Whenever jaundice was clinically noticed to be >10 mg/dl, bilirubin estimation was repeated immediately and then every day till 5 days of age and the highest reading was recorded as peak TSB.

Results: Significant hyperbilirubinemia (>17mg/dl) was present in 13% cases. At 24±6hours TSB >6 mg/dl was present in 47 cases and 26 of these developed hyperbilirubinemia (≥17 mg/dl) and TSB ≤6mg/dl was present in 153 cases, 2 of them developed significant hyperbilirubinemia. The incidence of hyperbilirubinemia in babies whose mothers received oxytocin and those whose mothers did not receive oxytocin was 19.6% and 8.2% respectively. The difference was highly significant. The mean values of TSB at 24±2 hrs in oxytocin used and oxytocin not used groups were 3.94±2.15 mg/dl and 3.36±1.91 mg/dl respectively, the difference was statistically significant but mean values of Peak TSB in oxytocin used and not used groups were. 12.78±4.28 mg/dl and 12.03±3.42 mg/dl respectively which was statistically not significant.

Conclusions: Incidence of significant hyperbilirubinemia in healthy babies is 13%. Use of oxytocin increased its incidence. TSB at 24±2hours ≤6mg/dl has a high predictive value in identifying those infants who are unlikely to develop subsequent hyperbilirubinemia. This study, thus, will help to discharge healthy term infants with TSB on 2nd day ≤6mg/dl.

Keywords: First-day serum bilirubin level; Neonatal hyperbilirubinemia; Significant hyperbilirubinemia; Oxytocin-induced hyperbilirubinemia

Introduction

Hyperbilirubinemia is a common and benign problem in neonates and is the most common cause of re-admission after hospital discharge. Almost all newborn infants have a serum or plasma total bilirubin (TB) level >1 mg/dL in contrast to normal adults in whom the normal TB level is <1 mg/Dl.

Approximately 85% of term neonates and most of the preterm neonates develop jaundice during the first week. Significant hyperbilirubinemia occurs in about 5- 10% of healthy term neonates [1]. Physiological jaundice usually appears on the 2nd – 3rd day, peaking between the 5th and 7th days of life. Jaundice may appear at birth or may appear any time during neonatal period depending upon the cause [2]. Since we know hyperbilirubinemia has a deleterious effect like Kernicterus, chore athetoid cerebral palsy, hearing impairment and cognitive impairment if not treated at the time. So meticulous screening of newborn is required to detect hyperbilirubinemia. Since the peak bilirubin level typically occurs at 72 to 96 hours, after healthy newborns are discharged from their birth hospital, follow-up is essential. Infants discharged before 72 hours should be seen within the next 2 days. Infants at lower gestational ages or who have other risk factors should be seen earlier [2]. This is practically impossible in underdeveloped and even in developing nations because of poverty, low education, and cultural practice. Here comes the role of prediction of neonatal hyperbilirubinemia.

Why the Need for Prediction?

In spite of jaundice being such a common and usually benign problem of neonates, pediatricians always have concern about it because of two specific reasons.

First, high level of unconjugated bilirubin is potentially neurotoxic and can lead to widespread brain damage, most severely to basal ganglia (kernicterus).

Second, conjugated bilirubin, though not neurotoxic, usually indicates some serious underlying pathology.

Hence an ability to predict becomes very important and life-saving in the context of a developing country like India and especially so in the state of Bihar, where costly investigations and regular follow-up is beyond the reach of the vast majority. So, this study has been proposed to help the doctors in the peripheral centers so that they can able to make a decision regarding the discharge of otherwise healthy neonates from their center.

Methods

This Prospective hospital-based study was conducted in Dept. of Paediatrics and Neonatology, Kurji Holy Family Hospital, Patna Bihar from 17 Jan. 2014 to 30th Nov. 2015. A total of 200 New-born, fulfilling the predefined inclusion criteria, delivered in our hospital were studied. Proper ethical and scientific clearance was taken from concerned hospital department. Proper consent was taken from Parents of babies after explaining the risks and benefits of neonatal jaundice, phototherapy, blood sampling.

Inclusion Criteria

Gestational age ≥ 37 wks (based on last Menstrual period).The absence of major congenital malformations.

Residing at Patna or nearby whose parents agree to come for follow up. Infants of Rh-negative mother would be included only if they are also Rh- negative.

Exclusion Criteria

Preterm (≤37 weeks) and post-term (≥42 weeks) neonates. Presence of significant illness (ie. sepsis & hypothyroidism). Rh incompatibility ABO incompatibility newborns with obvious life-threatening congenital malformation (trachea- esophageal fistula (TOF), anorectal malformation).

Babies with conjugated hyperbilirubinemia: All babies delivered in KHFH were examined and a detailed antenatal and postnatal history was taken. Cases were selected if they fulfilled all the criteria set out above. Informed consent was taken from the parents and blood was collected from the venous site. The blood sample of the mother was simultaneously collected and sent for Blood Grouping if it was not known from before. The blood sample of the infant was sent for grouping and TSB estimation.

All babies were breast feed as soon as possible after birth. As per discharge policy KHFH healthy vaginally delivering mothers were discharged the next day. Hence parents were instructed to bring their neonates for clinical follow up every day and to report as soon possible if they noticed yellowness of skin. However, in case of mothers delivering by Caesarean Section, the neonates could be followed up clinically on a daily basis since patients were discharged only after seven days. At 5 days of age, another venous sample was collected for TSB estimation.

Whenever jaundice was clinically noticed to be >10 mg/dl, bilirubin estimation was repeated immediately and then every day till 5 days of age and the highest reading was recorded as peak TSB. Serum bilirubin >17mg/dl was considered significant hyperbilirubinemia. Babies having significant hyperbilirubinemia were admitted in NICU for treatment (Phototherapy). Clinical Assessment of Jaundice was done according to Kramer's Rule [13]. Jaundice in face – TSB > 5mg/dl. Jaundice in trunk – TSB between 10 and 15mg/dl Jaundice in palms and soles – TSB > 15 mg/dl.

Bilirubin Estimation

The Serum Bilirubin was estimated by micro-bilirubin (Jendrassik & Grof method) for that venous blood is taken in four microcapillaries and centrifuged at the rate of 10000 rpm for 5 minutes. Bilirubin estimation is done spectrophotometrically using beam method (55 nm wavelength) (micro la-300, Merck, Netherland). Calibration of bilimeter is done daily using labeteral solution.

Statistical Analysis

Data Analysis was carried out using Microsoft excel sheet. In case of Quantitative data, mean and standard deviation, as well as range (minimum & maximum value), is computed. For qualitative data, independence of variable/attributes is tested with the help of $\chi 2$ (Chi-square test). Sensitivity, specificity, positive and negative predictive value of different cut-points of 24±6hr, serum bilirubin is obtained. For determining the significance of each test p-value of <0.05 was used.

Results

The total number of cases studied was 200. Out of which 181 cases were delivered by Caesarean and 19 vaginally. 123 (61.5%) were males and 77(38.5%) were females; oxytocin had been used in 102 (51%) cases.

The incidence of clinical jaundice was 56%. Significant hyperbilirubinemia (>17mg/dl) was present in 13% cases. At 24±2 hours TSB >6 mg/dl was present in 47 cases and 26 of these developed hyperbilirubinemia (≥17 mg/dl) and TSB≤6mg/dl was present in 153 cases, 2 of them developed significant hyperbilirubinemia. The incidence of hyperbilirubinemia in babies whose mothers received oxytocin and those whose mothers did not receive oxytocin was 19.6% and 8.2% respectively and the difference was highly significant. The mean values of TSB at 24±2 hrs in oxytocin used and oxytocin not used groups were 3.94±2.15 mg/dl and 3.36±1.91 mg/dl respectively, the difference was statistically significant but mean values of Peak TSB in oxytocin used and not used groups were 12.78±4.28 mg/dl and 12.03±3.42 mg/dl respectively which was statistically not significant.

Discussion

Neonatal jaundice is a very common occurrence and poses a therapeutic dilemma to the pediatrician. As such it is highly desirable to have a parameter to predict which babies are subsequently going to develop a significant level of bilirubinaemia. The present study was designed to investigate whether a TSB level ≤6mg/dl at 24±2hours can predict weather children will or will not develop significant hyperbilirubinemia (≥17mg/dl) and hence can be safely discharged.

In our study caesarean section was the prominent mode of delivery. Caesarean deliveries accounted for 90.5% of the study group and vaginal deliveries accounted for 9.5%. Such a significantly high incidence of Caesarean deliveries is because of the design of the study. The attrition rate (i.e. cases who were lost to follow up and did not report on the fifth day) was quite high (=20%). All of these cases, which were lost to follow up were accounted for by vaginal deliveries. This led to an increased percentage of caesarean deliveries in the final list.

Oxytocin was used in a significant proportion of the deliveries (=51%). It was used in 47.5% of the Caesarean deliveries and in 84.22% of vaginal deliveries. This was in accordance with the management policies of the Labour Room unit. Table 1 shows the percentage of cases that developed clinical jaundice and cases who developed significant hyperbilirubinemia (i.e. Peak TSB ≥17mg/dl).

Total enrollments	Clinical Jaundice Present	Percentage	Significant Hyperbilirubinemia (≥17 mg/dl)	Percentage
200	112	56	26	13

Table 1: Incidence of Clinical Jaundice and significant Hyperbilirubinemia.

Clinical jaundice was noticed in 56% of the cases. This is in accordance with the figure quoted by most authorities on the subject: Avery's text book of neonatology [3]. In our study significant hyperbilirubinemia developed in 13% of the cases. Previous studies which showed similar results are: Guaran, et al. found in a retrospective study of 88000 live born infants in Australia incidence of significant hyperbilirubinemia (>12mg/dl) as 12.4% [4]. Awasthi and Rehman et al. in a review of 274 neonates from North India had found the incidence of hyperbilirubinemia (>15 mg/dl) to be 12.3% [5]. Shivani Ramdev, et al. reviewed 200 neonates from IGMC Department of Neonatology, Shimla & found the incidence of hyperbilirubinemia ≥17mg% beyond 77hr of life is 12% [6].

Table 2 compares the incidence of hyperbilirubinemia in infants who had TSB ≤6mg/dl at 24 hours with those who had TSB >6mg/dl at 24 hours. A TSB of ≤6mg/dl was present in (76.5%) of the cases. Out of these only 1.3%, infants developed hyperbilirubinemia. TSB >6mg/dl at 24 hrs was present in 23.5% cases and 55.32% of these subsequently developed hyperbilirubinemias. The sensitivity of TSB >6 mg/dl in detecting which infants will develop hyperbilirubinemia was found to be 92.86%; Specificity of the test was 87.79%; the Positive predictive value of the test was 55.31%; the Negative predictive value of the test was 98.69%. These statistical figures therefore, shows that if neonate has TSB ≤6 mg/dl at 24 hours there is decreased risk of development of hyperbilirubinemia (≥17 mg/dl) subsequently. Thus, it will be justifiable for doctors attending the nursery to discharge such infants. These results were comparable with the study by Agarwal, et al. 2002 [7]. They had found the sensitivity of TSB >6 mg/dl at 24 hours was 95%, specificity 70.6%, PPV 27.2%, NPV 99.3%. They followed the neonates clinically till discharge at 72 hours and again at 5 days. Jaundice was assessed clinically by two DM fellows and TSB estimation was done for only those infants in whom the assessment of jaundice was more than 10 mg/dl. This design carried the possibility of error inherent in clinical assessment and there were chances of missing some cases. In the present study, this problem was bypassed by the universal screening of all enrolled infants for TSB at 5 days.

TSB at 24±2 hrs.	No. of cases who developed TSB ≥17 mg/dl	No. of cases who did not develop TSB≥17 mg/dl	Total
>6 mg/dl	26 (a)	21 (b)	47
≤6 mg/dl	2 (c)	151 (d)	15
Total	28	172	200
Sensitivity:		a /a+c	92.86%
Specificity:		d/d+b	87.79%
Positive predictive value:		a/a+b	55.31%
Negative predictive value:		d/d+c	98.69%

Table 2: Distribution of Hyperbilirubinemia cases.

In the present study, the mean age at the discharge of babies who were delivered vaginally was 24.0±1.2 hours. Of the vaginally delivered babies, only 2% turned up for clinical follow-up regularly. There is thus a theoretical risk in the rest that there might have been the transient elevation of TSB above 17 mg/dl, which had come down by the 5th day and thus some cases might have been missed. This risk was also present in the study by Agarwal, et al. but the risk was higher in the present study because of the longer duration of intervals between the assessments [7]. However, as Agarwal, et al comment "Even if this did happen this should not be a cause for concern in real life situations". Alpay, et al. found the sensitivity and specificity of First day TSB ≥6 mg/dl to be 100% each in predicting the development of significant hyperbilirubinemia [8]. Awasthi, et al. showed that TSB level of 3.99 mg/dl at 18-24 hours was able to predict subsequent hyperbilirubinemia (>15 mg/dl) with a sensitivity and specificity of 67% each [5].

The differences from this study were probably due to the different design of the study. In their study complete follow up was present in infants who stayed in the hospital for some neonatal or maternal illness. Bhutani, et al. demonstrated in a large cohort that hour specific nomograms can predict which infants are at high risk for subsequent hyperbilirubinemia [9]. Pre-discharge 6.1% of the study population hadbilirubin values in the high-risk zone (>95th percentile) and 61.8% cases were in low-risk groups (<40th percentile). They showed that in this low-

risk group there was no measurable risk of significant hyperbilirubinemia. When the results of the present study were plotted on the nomogram developed by them, 83% of the infants were classified in the low-risk zone. 2% of the cases fell in the high-risk zone and the rest 15% cases fell in intermediate risk.

Table 3 compare mode of delivery with respect to the incidence of hyperbilirubinemia, mean TSB values at 24 hours and mean Peak TSB values. A statistically significant difference was found in the values between Caesarean and vaginal deliveries, with vaginal deliveries having higher incidence.

Group	TSB at 24±2 hrs.			Peak TSB level			No. of babies who developed TSB ≥17 mg/dl	No. of babies who did not develop TSB ≥17 mg/dl	Total
	Range	Mean	SD	Range	Mean	SD			
Caesarean	1.0 – 9.2	3.56	1.97	2.4 – 24.0	12.32	3.66	22 (12.2%)	159 (87.8%)	181
Vaginal	0.8 – 8.6	4.57	2.59	2.30 - 21.2	13.27	5.69	6(31.6%)	13(68.43%)	19
	t = 2.05 P<0.05 Significant			t = 1.01, P>0.05 not significant			χ2(Chi-square)=5.39,df=1, P<0.05 significant.		200

Table 3: Compares the TSB at 24±2 hrs and Peak TSB levels incidence of Hyperbilirubinemia amongst Caesarean and Vaginal deliveries.

Table 4 compares the incidence of hyperbilirubinemia based on whether the mother received or did not receive oxytocin, the mean TSB at 24 hours and Peak TSB between these groups. In Oxytocin used and Oxytocin not received groups Mean TSB at 24±2hours was 3.44±2.15 and 3.36±1.91 and mean Peak TSB level was 12.78±4.28 and 12.03±3.42 respectively. In oxytocin and not oxytocin received groups the difference was found to be significant.

Group	TSB at 24±2 hrs.			Peak TSB level			No. of babies who developed TSB ≥17 mg/dl	No. ofbabies who did not developTSB ≥17 mg/dl	Total
	Range	Mean	SD	Range	Mean	SD			
Oxytocin used	0.8 – 9.2	3.94	2.15	2.3 – 24.0	12.78	4.28	20 (19.6%)	82 (80.4%)	102
Oxytocin not used	1.0 – 8.3	3.36	1.91	2.4 – 21.9	12.03	3.42	8 (8.2%)	90 (91.8%)	98
	't' = 2.01 'P'<0.05 Significant			't' = 1.37 'P'>0.05 Not significant			χ^2 (Chi-square) = 5.44, df = 1, P<0.05 significant.		200

Table 4: Compares the TSB at 24±2 hrs and Peak TSB levels & incidence of Hyperbilirubinemia oxytocin used and not used groups.

Comparison showed the significant difference between the two groups in the mean TSB at 24±2hours but no significant difference in the mean Peak TSB levels. These findings are in accordance with those of Ghosh and Hudson [10]. In their study of 197 babies, 94 deliveries took place without oxytocin being given. Of these only, 6% developed hyperbilirubinemia (>12 mg/dl). Of the 103 deliveries in which oxytocin were given, 17.4% babies developed hyperbilirubinemia. Davies et al. had also found the significant difference between the two groups with respect to TSB levels at the 2nd day as well as 5th day [11]. However, in the present study, the difference was significant only with respect to mean TSB levels at 24±2hours. This variation may be related to the dose and duration of oxytocin drip [12-17].

Conclusion

To conclude, our study showed the incidence of significant hyperbilirubinemia in healthy babies is 13%. The incidence is increased by the use of oxytocin. TSB at 24±2hours ≤6mg/dl has a high predictive value in identifying those infants who are unlikely to develop subsequent hyperbilirubinemia subsequently. The importance of this study is that it will help pediatricians and doctors posted in the nursery in planning an early

discharge of healthy term new-borns. Thus, they will be justified in discharging healthy term infants with TSB on 2nd day ≤6mg/dl early.

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