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# Prediction of Significant Neonatal Hyperbilirubinemia on The Basis of Cord Serum Albumin Level in Healthy Term Neonates.

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***Abstract***
*Objective: To study the association of cord serum albumin (CSA) level with incidence of neonatal hyperbilirubinemia (NNH) in term neonates.*
*Method: We conducted a prospective study on 100 sequentially born term babies. Cord blood collected at birth was analyzed for estimation of serum albumin. After a follow up of 3 days, venous sample was taken at 72 hrs of age and analyzed for total serum bilirubin (TSB) level. A value of TSB ≥17 mg/dl at 72 hours of life was taken as significant NNH. Neonates were divided into 3 groups according to their cord serum albumin (CSA) levels; group A with CSA <2.8 gm/dl, group B with CSA 2.8-3.3 gm/dl and group C with CSA >3.3 gm/dl and incidence of significant hyperbilirubinemia was studied in all these groups.*
*Results: There were 13 neonates in groups A , 57 in group B and 30 in group C. Out of 13 neonates in group A, 5 (38.5%) developed significant NNH; in group B, 7 (12.3%) out of 57 neonates developed NNH whereas in group C, 2 (6.7%) neonates out of 30 developed NNH. This difference in the incidence of significant NNH amongst the three groups was statistically significant (p=0.02). We also calculated and compared mean day 3 TSB levels of the three groups. The mean day 3 TSB level was highest in group A (14.6±3.62 mg %), 12.1±3.25 mg% in group B and lowest (11.0±3.28 mg %) in group C. On comparing these means by ANOVA, statistically significant difference was found (p=0.005).*
*Conclusion: High CSA level is associated with a lower incidence of significant NNH. Hence, this can be used as a potential tool for prediction of hyperbilirubinemia in neonates.*
***Keywords:*** *Neonatal hyperbilirubinemia, Cord serum albumin, Total serum bilirubin.*

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## I. Introduction

Jaundice is one of the most common conditions that require medical attention in newborns. The yellow coloration of skin and sclera in newborns with jaundice is the result of accumulation of unconjugated bilirubin. Adults appear jaundiced when the total serum bilirubin level exceeds 2.0 mg/dl while newborns appear jaundiced when it is >7mg/dl [1]. Clinical jaundice is seen in 60-70% of term and in about 80% of preterm newborns [2]. A serum bilirubin value over 15 mg% is found in 3% of normal term newborns [1].

Early discharge of healthy term newborns after normal vaginal delivery has become a common practice nowadays, because of certain medical and social reasons and also due to economic constraints making recognition, follow up and early treatment of jaundice more difficult [3]. American Academy of Pediatrics recommends that newborns discharged within 48 hours should have a follow-up visit after 48 to 72 hours for any significant jaundice and other problems [4].This recommendation is not feasible in our country due to limited follow-up facilities in the community. These earlier discharged babies may develop jaundice which may be over-looked by the caretakers causing delay in seeking medical advice and hence development of complications; the most important being bilirubin induced brain damage even in healthy term infants. Though exact serum bilirubin level that leads to development of kernicterus in icteric newborn is not known, serum bilirubin level more than 20 mg/dl is likely to be toxic and may cause significant damage to brain [1]. It is also noteworthy that the most common cause for readmission during the early neonatal period is hyperbilirubinemia. Hence, by predicting early at birth, the newborns who can develop significant neonatal jaundice, we can design and implement the follow-up program in the high risk groups effectively [5].

In this regard, if we look upon the metabolism of bilirubin in the human body, albumin helps in hepatic transportation of bilirubin and its clearance. Low serum albumin level will decrease bilirubin clearance and thus will increase the chances of significant hyperbilirubinemia. Hence it can be hypothesized that cord serum albumin levels can predict significant hyperbilirubinemia [6].

The study done by Suchanda Sahu et al showed the prediction of significant hyperbilirubinemia by measuring cord blood albumin. 82% of neonates who had cord blood albumin level <2.8g/dl developed hyperbilirubinemia requiring phototherapy and 12% needed exchange transfusion. Neonates with cord blood albumin level>3.3g/dl didn't develop significant hyperbilirubinemia [7].

Similar study was done by Meena KJ et al on 100 neonates. Neonates were divided into 3 groups A, B, and C according to cord blood albumin levels < 2.8 gm/dl, 2.8-3.3 gm/dl and >3.3 gm/dl respectively and then followed up clinically for the development of jaundice upto day 5 of life. In group A, 21 (95.5%) neonates developed jaundice, of which 18 (81.8%) required phototherapy and 2 (9.1%) needed exchange transfusion; whereas 27 (79.4%) neonates in group B developed jaundice, of which 9 (26.6%) needed phototherapy and none required exchange transfusion. In group C, 16 (36.6%) developed jaundice of which 1 (2.4%) required phototherapy and none of them required exchange transfusion (p value <0.001) [8].

There is still paucity of studies in this direction hence we decided to conduct this study to find out the efficacy of cord serum albumin as a predictor of significant neonatal hyperbilirubinemia.

## II. Material and Methods

**Study Design:-**

This is a hospital based prospective study.

**Study location:-**

The present study was conducted in the Department of Pediatrics, SDM hospital in active collaboration with the Department of Obstetrics and Gynecology, SDM hospital, Jaipur. Ethical clearance was obtained from the institutional ethical committee.

**Sample size and study duration:-**

Sample size was calculated at 90% study power and α error of 0.05, assuming occurrence of NNH in 95.5%, 79.4%, 36.4% newborns in group A (CSA < 2.8 gm/dl), group B (CSA 2.8-3.3 gm/dl) and group C (CSA>3.3 gm/dl) respectively in the similar study conducted by Meena KJ et al in 2015 [8].

Following the above assumption, a minimum of 45 neonates were required as sample size but it was enhanced and rounded off to 100 neonates to enhance power and validity of study.

Study was conducted on sequentially born normal neonates delivered at Santokba Durlabhji Memorial Hospital, Jaipur from December 15, 2015 – May 23, 2016 and interpretation of results was done in the next one month.

**Selection method:**

**Inclusion criteria**

- Term babies (both genders)
- Mode of delivery- normal and caesarean section
- Birth weight > 2.5kg.
- APGAR > 7/10 at 1 min.

**Exclusion criteria**

- Preterm babies (<37 weeks).
- All isoimmunization (Rh & ABO incompatibility).
- Neonatal sepsis.
- Instrumental delivery (forceps and vacuum).
- Birth asphyxia.
- Respiratory distress.
- Meconium stained amniotic fluid.

Informed parental consent was taken from all cases. Cord blood collected at birth was analyzed for estimation of serum albumin by Bromcresol green dye binding measured by reflectance spectrophotometry, serum bilirubin by colorimetric measurement of Azobilirubin chromophore and baby's blood group. Complete hemogram, Peripheral blood film examination, Reticulocyte count, Septic screen, G6PD Levels and thyroid function tests were also sent if required. All enrolled babies were followed up daily for 3 days and clinical assessment for jaundice was done according to Kramer dermal scale. Under aseptic precautions, 1 ml of venous blood was drawn from all the babies enrolled in the study at 72 hours of life, for estimation of TSB. A value of TSB ≥17 mg/dl at 72 hours of life was taken as significant NNH needing intervention as per the AAP guidelines 2004.

**Statistical Analysis:-**

The main outcome of the study was inferred in terms of significant NNH. All data collected were entered in excel sheet to prepare master chart. Continuous variables were summarized as mean and standard deviation, while nominal/categorical variables as percentage. Categorical variables related to baseline

characteristics of enrolled neonates were analyzed for their distribution among different groups according to CSA level and day 3 TSB. Chi square test was used to assess the difference at significance level (p value < 0.05).

Bivariate analysis was used to determine association of occurrence of significant NNH among the categories of CSA level. Statistical significance of the association was assessed using chi square test at p value 0.05. Distribution of day 3 TSB level was also analyzed by Box-and-Whisker plot with respect to all three CSA level categories.

For assessing association between day 3 TSB levels and CSA level categories, we applied one way ANOVA test and homogeneity of variances of different independent groups was tested by Levene's test. P value of <0.05 was taken as significant. Openepi, web based, open source software developed by center for disease control and prevention (CDC), was used for all statistical calculations.

## III. Results

In our study, 100 enrolled neonates were divided into 3 groups according to their CSA levels; group A with CSA <2.8 gm/dl, group B with CSA 2.8-3.3 gm/dl and group C with CSA >3.3 gm/dl. Distribution of cases according to all the baseline characteristics (gender, mode of delivery, gestational age, parity and birth weight) were similar and comparable in the all three groups (Table no. 1). We also compared the baseline parameters of neonates who developed significant NNH with those neonates who did not develop significant NNH on day 3 of life. Even amongst these two groups, these parameters were found to be similar with p value >0.05 in all (Table no. 2).

The outcome of our study was inferred in terms of incidence of significant NNH on day 3 in the enrolled neonates. Significant NNH occurred in a total of 14 subjects on day 3 of life. In group A, 5 neonates (38.5%); in group B, 7 neonates (12.37%) and in group C, 2 neonates (6.7%) developed significant NNH. As the p value (0.02) suggests, this difference in the incidence of significant NNH was statistically significant (Table no. 3), which indicates that CSA levels are useful in predicting subsequent NNH in healthy term neonates.

We have also calculated the mean & median of day 3 TSB levels & compared them among the three groups A, B and C, as depicted by table no. 4. The mean level of TSB on day 3 of life was 14.6 ± 3.62 mg% in group A, 12.1 ± 3.25 mg% in group B and 11.0 ± 3.28 mg% in group C.

**Table no 1:** Shows basic characteristics of all groups based on CSA levels.

| | | Group A (n=13) | Group B (n=57) | Group C (n=30) | $X^2$ | p value |
|---|---|---|---|---|---|---|
| Gender | Male | 6 (12.2%) | 26 (53.1%) | 17 (34.7%) | 1.01 | 0.60 |
| | Female | 7 (13.7%) | 31 (60.8%) | 13 (25.5%) | | |
| Mode of delivery | NVD | 6 (9.20%) | 39 (60.0%) | 20 (30.80%) | 2.36 | 0.31 |
| | CS | 7 (20.0%) | 18 (51.4%) | 10 (28.6%) | | |
| Gestational age | 37 weeks | 4 (18.2%) | 9 (40.9%) | 9 (40.9%) | 10.12 | 0.12 |
| | 38 weeks | 5 (16.1%) | 19 (61.3%) | 7 (22.6%) | | |
| | 39 weeks | 3 (10.3%) | 14 (48.3%) | 12 (414%) | | |
| | ≥40 weeks | 1 (5.6%) | 15 (83.3%) | 2 (11.1%) | | |
| Parity | Para1 | 8 (11.9%) | 41 (61.2%) | 18 (26.9%) | 1.52 | 0.82 |
| | Para2 | 3 (15%) | 10 (50%) | 7 (35%) | | |
| | ≥Para3 | 2 (15.4%) | 6 (33.3%) | 5 (27.8%) | | |
| Birth weight | Up to 50$^{th}$ percentile | 10 (17.5%) | 29 (50.9%) | 18 (316%) | 2.83 | 0.24 |
| | More than 50$^{th}$ percentile | 3 (7.0%) | 28 (65.1%) | 12 (27.9%) | | |

**Table no 2:** Shows basic characteristics of both groups based on significant NNH.

| | | Significant NNH | | $X^2$ | p - Value |
|---|---|---|---|---|---|
| | | YES n (%) | NO n (%) | | |
| Mode of delivery | Normal vaginal delivery | 8 (12.3%) | 57 (87.7%) | 0.44 | 0.51 |
| | LSCS | 6 (17.1%) | 29 (82.9) | | |
| Gestational age | 37 weeks | 2 (9.0%) | 20 (91.0%) | 3.40 | 0.33 |
| | 38 weeks | 7 (22.6%) | 24 (77.4%) | | |
| | 39weeks | 4 (13.8%) | 25 (86.2%) | | |

| | | | | | |
|---|---|---|---|---|---|
| | ≥40 weeks | 1 (5.0%) | 17 (95%) | | |
| Sex | Male | 7 (13.7%) | 44 (83.3%) | 0.007 | 0.93 |
| | Female | 7 (14.3%) | 42 (85.7%) | | |
| Parity | Para1 | 9 (13.4%) | 58 (86.6%) | 0.06 | 0.97 |
| | Para2 | 3 (15.0%) | 17 (85.0%) | | |
| | Para3 or more | 2 (15.4%) | 11 (84.6%) | | |
| Birth weight | Up to 50$^{th}$ percentile | 11 (19.0%) | 47 (81.0%) | 2.82 | 0.09 |
| | More than 50$^{th}$ percentile | 3 (7.1%) | 39 (92.9%) | | |

**Table no. 3:** Incidence of significant NNH in the three groups A, B and C

| | Significant NNH | | $X^2$ | p-value |
|---|---|---|---|---|
| | YES n (%) | NO n (%) | | |
| Group A | 5 (38.5%) | 8 (61.5%) | 7.94 | 0.02 |
| Group B | 7 (12.3%) | 50 (87.7%) | | |
| Group C | 2 (6.7%) | 28 (72%) | | |

**Table no. 4:** Statistical parameters for day 3 TSB levels in three groups A, B and C

| | Day 3 TSB levels | | | | |
|---|---|---|---|---|---|
| Group (n) | Mean | Median | Std. Deviation | Std. Error of mean | Range |
| Group A (13) | 14.63 | 15.40 | 3.62 | 1.00 | 11.6 (10.0-21.6) |
| Group B (57) | 12.09 | 11.30 | 3.25 | 0.43 | 13.8 (6.4-20.2) |
| Group C (30) | 10.97 | 10.65 | 3.28 | 0.60 | 14.6 (4.0-18.6) |

ANOVA done for assessing association of different CSA levels with day 3 TSB levels between groups and within groups showed significant difference (p=0.005), indicating that there was statistically significant difference between the mean of day 3 TSB level in the three groups A, B and C (Table no. 5). Before applying ANOVA test, homogeneity among independent groups was tested non significant by levene's test.

**Table no 5:** ANOVA for difference between mean of day 3 TSB for groups A, B and C.

| **ANOVA Table** | | | | |
|---|---|---|---|---|
| Source of variation | Sum of squares | df | *F* statistics | p-value |
| Between Groups | 121.70 | 2 | 5.56 | 0.005 |
| Within Groups | 1061.22 | 97 | | |
| Total | 1182.91 | 99 | | |

Box & whisker plot in figure 1 shows the graphical comparison of day 3 TSB levels in groups A, B and C. The middle line in the box denotes the median value, the lower and upper ends of the boxes signify 25$^{th}$ and 75$^{th}$ centiles, while the bars outside denote the range for the day 3 TSB levels. The median level of day 3 TSB is highest in group A, and lowest in group C, thus showing the inverse association of CSA levels with levels of TSB on day 3 of life.

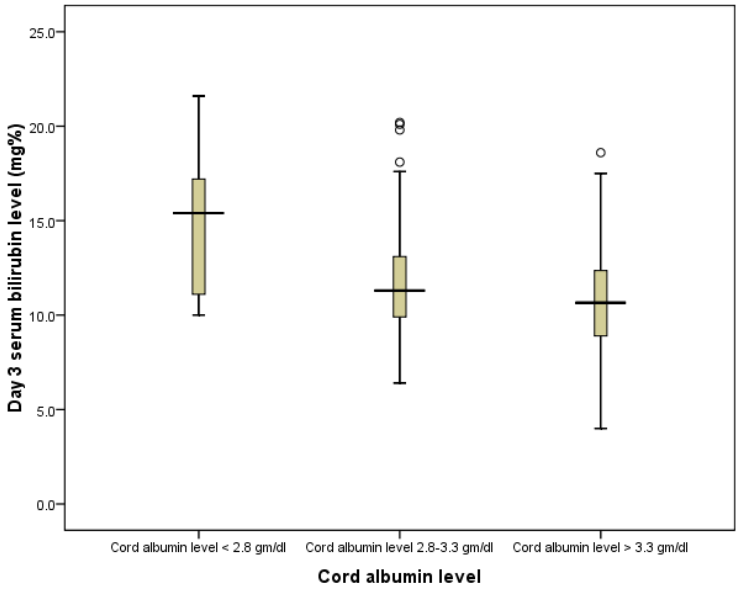


**Fig.1:** The box & whisker plot showing day 3 TSB levels in group A, B and C.

## IV. Discussion

NNH is a common neonatal problem with the dreaded complication of bilirubin induced neurological dysfunction (BIND), due to entry of free bilirubin into the brain. The complications usually occur when the hyperbilirubinemia goes unrecognized by the care-takers and presents late to the pediatrician due to early discharge of the newborns after delivery and poor follow-up. So prediction of significant NNH in healthy term neonates early in life becomes important so that the neonates at risk can be followed up closely and early treatment can be instituted.

Albumin binds to unconjugated bilirubin (UCB) and helps in its transportation to the liver and clearance. Low levels of albumin will decrease bilirubin clearance and increase free bilirubin levels in the circulation leading to the chances of significant NNH and its complications. This concept formed the basis of our study in which we have tried to study the prediction of significant NNH by the level of cord serum albumin in term neonates.

Day 3 was chosen for assessment for significant NNH in our study since most of the previous studies have noticed that the onset of jaundice is on day 3 of life in majority of neonates. In the study by Meena KJ et al [8], neonates were followed up daily till day 5 of life and they found that the onset of jaundice in majority of neonates was on day 3. Sethi et al also reported the development of jaundice on day 3 of life in 2/3$^{rd}$ of neonates [9].

The first study done by Sahu S et al [7] inducted 40 newborns in their study; while another study by Trivedi DJ et al [10] evaluated 605 newborns and studied CSA as an additional risk indicator in predicting NNH. In the study by Sahu S et al [7], 14 out of 17(82.35%) neonates in the group with CSA <2.8 gm/dl developed NNH; all of them requiring phototherapy and two of them (11.8%) requiring exchange transfusion. The group with CSA between 2.8 – 3.3 gm/dl had a lesser incidence, that is, 6 out of 15 (40%) and they all were treated with phototherapy. None of the babies with CSA>3.3 gm/dl developed NNH requiring any intervention. Thus they concluded that CSA level more than 3.3 gm/dl is possibly safe for early discharge of babies.

In another study done by Meena KJ et al [8], 21 (95.5%) out of 22 neonates in group A, 27 (79.4%) out of 34 neonates in group B and 16 (36.6%) out of 44 neonates in group C developed jaundice as visually assessed by Kramer's criteria (Kramer dermal zone ≥ 3). The drawback of this study may be that the patients developing jaundice may be over-estimated or at times missed due to subjective errors associated with visual assessment. Out of 21 neonates developing NNH in group A, 18 (81.8%) required phototherapy and 2 (9.1%) required exchange transfusion. In group B, out of 27 neonates developing NNH, only 9 (26.6%) required phototherapy and none required exchange transfusion; while in group C out of 16 neonates developing NNH only 1 (2.4%) required phototherapy and none required exchange transfusion.

Similarly in the study of Trivedi DJ et al [10], out of 605 neonates, 205 (33.88%) developed NNH within first 7 days of life; out of which 120 (58.33%) babies had CSA level <2.2 gm/dl, 59 (28.78%) babies with CSA level in the range of 2.8–3.5 gm/dl developed NNH whereas 26 (12.68%) babies developed NNH even though CSA level was >3.5 gm/dl.

In addition to the above findings, we also calculated and compared mean day 3 TSB level of the three groups. The mean day 3 TSB was highest in group A (14.6±3.62 mg %), 12.1±3.25mg % in group B and lowest (11.0±3.28mg %) in group C in our study. On comparing these means by ANOVA, statistically significant difference was found (p=0.005). No other previous study compared the mean day 3 TSB level of the three groups which is another powerful indicator of the importance of CSA level in predicting NNH and is one of the strengths of our study.

We also calculated median day 3 TSB levels of three groups and plotted them on a box and whisker plot which clearly demonstrated that the median level of day 3 TSB was highest in group A and lowest in group C, thus strengthening the association.

## V. Conclusion

The present study infers that cord serum albumin level is effective to pick up babies at risk of developing significant neonatal hyperbilirubinemia. A CSA value of more than 3.3 gm/dl is safe for discharging the newborns early from hospital while a value less than 3.3 gm/dl alerts the pediatrician for close follow-up.

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