Original Research Article

Cord serum albumin as a predictor of neonatal hyper bilirubinemia in healthy full-term neonates

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Abstract

Introduction: Neonatal jaundice or icterus neonatorum is one of the common problem that is seen in newborns during first week of neonatal life. Clinical jaundice is found in about 80% of preterm and in about 60-70% of term neonates. The main objective of the study was to determine the correlation between cord serum albumin levels and development of significant hyper bilirubinemia in healthy term neonates. **Methods:** A prospective study was conducted on 316 healthy term neonates. Gender, mode of delivery and birth weight were taken into consideration. It was ascertained that there was no other risk factor for neonatal hyperbilirubinemia among these newborns. These neonates were divided into 3 groups, Group A (cord serum albumin levels < 2.8 gm/dl), Group B (cord serum albumin levels between 2.8 to 3.4 gm/dl) and Group C (cord serum albumin levels > 3.4 gm/dl). **Result:** Of the 316 babies included in the study, 102 babies were under Group A, 166 babies under Group B and 48 babies under Group C. 35 babies in Group A, 5 in Group B and none in Group C developed significant hyperbilirubinemia and required phototherapy. The sensitivity and specificity of cord serum albumin level < 2.8 g/dl to predict risk of development of significant neonatal hyperbilirubinemia in our study was 87.50% and 75.72% respectively. **Conclusion:** Cord serum albumin levels can help us to predict the possibility of significant hyperbilirubinemia among neonates. Hence this can help us to identify the at-risk neonates and utilize our limited resources efficiently among these newborns.

Keywords: Cord serum albumin, Hyperbilirubinemia, Icterus neonatorum

Introduction

Neonatal jaundice or icterus neonatorum is one of the common problems that are seen in newborns during first week of neonatal life [1]. Clinical jaundice is found in about 80% of preterm and in about 60-70% of term neonates [2]. More than 6.1% of term neonates were found to have bilirubin level more than 12.9 mg/dl and 3% of term neonates had bilirubin level more than 15 mg/dl [3]. In India incidence of neonatal hyper bilirubinemia varied from 4.3% to 6.5% of all live born babies [4]. Neonatal hyper bilirubinemia is the commonest cause of readmission in early neonatal period in about 6.5% cases [1].

In current clinical practice, healthy term newborns after normal delivery are discharged earlier due to either medical reasons to prevent them from nosocomial infections, social reasons like early naming ceremony or due to financial constrain. As per American Academy of Pediatrics Recommendations, the new borns discharged before 48 hours of birth should be followed between 48 to 72 hours of birth to rule out significant neonatal jaundice and other problems [5]. In our country because of limited follow up facilities such close monitoring is usually not feasible and due to poor follow up, sometime the newborn with significant neonatal jaundice may be missed or the treatment delayed, resulting in brain damage of these newborn.

The main concern regarding early discharge are reports of bilirubin induced brain damage in healthy term neonates even without hemolysis. Though the exact total serum bilirubin (TSB) level that leads to development of kernicterus in icteric newborn is not known, A bilirubin level greater than 20 mg/dl is found to be associated with development of kernicterus and

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may cause severe form of brain damage [1]. Defining a certain bilirubin level as physiological can be misleading and potentially dangerous. It is difficult to predict the course of hyperbilirubinemia on day one of a neonate. The concept of prediction of jaundice offers an attractive option to pick up babies at risk of developing significant neonatal hyperbilirubinemia.

Till date only few predictors of neonatal jaundice have been studied, these are cord blood albumin, cord blood bilirubin, cord blood albumin to bilirubin ratio and alpha-fetoprotein [6]. By predicting the newborns developing significant neonatal jaundice early at birth, we can design and implement the follow-up of the high-risk groups cost effectively. In this way early treatment could be started, which could reduce the risk of bilirubin dependent brain damage. There is paucity of studies on cord serum albumin (CSA) as a predictor of severity of neonatal hyper-bilirubinemia, hence our study was aimed to evaluate the predictive value of cord serum albumin as predictor of significant neonatal hyperbilirubinemia in healthy term neonates and subsequent requirement of phototherapy or exchange transfusion.

Materials and Methods

Study design- Prospective study

Study center- Department of Pediatrics, Maharishi Markandeswar Institute of Medical Sciences and Research (MMIMSR) Mullana, Ambala (Haryana)

Period of study- September 2015 to February 2017

Ethical clearance was obtained from the institutional ethical committee.

Sample size- When the prevalence of neonatal jaundice patients was assessed with precision error of estimation (d) = 0.03, and alpha =0.05, a sample size of at least 100 cases was needed to estimate the incidence.

Study population- The study was conducted on 316 healthy newborns with the following criteria

Inclusion criteria

- Term newborns
- Birth weight ≥ 2.5 kg.
- APGAR ≥7/10 at 1 min

ExclusionCriteria

- Preterm,
- Out born neonates
- Rh incompatibility
- ABO incompatibility
- Instrumental delivery (forceps and vacuum)
- Hemolyticanemia(G6PD,Hereditaryspherocytosisetc)
- Birth asphyxia
- Newborn with major congenital malformation,
- Neonatal sepsis
- Neonatal jaundice within 24 hours of life
- Neonatal hypothyroidism
- Meconium aspiration and babies on drugs like phenobarbiturates

Methodology and Sampling method- A detailed maternal and neonatal history was taken as per the prescribed Performa. The recruited mother of the neonates were assessed in detail as regards the gestational age, blood group, parity, oxytocin infusion, maternal risk factors like premature rupture of membrane, meconium stained liquor, sepsis, fever, oligo-hydroamios, and mode of delivery. The clinical examination of the newborn was done at the time of delivery and thereafter regularly during the hospital stay.

2 ml of umbilical cord blood as collected from all newborns included in my study and measurement of cord serum albumin levels is done by an auto analyzer "SIEMENS Dimension clinical chemistry system Flex reagent cartridge Albumin method".

Based on the levels of cord serum albumin these neonates were further divided into 3 groups:
CSA Group A: Cord serum albumin levels < 2.8 gm/dl
CSA Group B: Cord serum albumin levelsbetween2.8 to 3.4 gm/dl
CSA Group C: Cord serum albumin levels > 3.4 gm/dl

The normal range for cord serum albumin in term babies is 2.8 – 3.4 gm/dl.

For estimation of total serum bilirubin (TSB) 2 ml of venous blood from babies included in the study was collected at 24 hours, between 3-5 days and thereafter if required for estimation of total serum bilirubin and results were obtained by automatic analyzer "SIEMENS Dimension clinical chemistry system Flex reagent cartridge Total Bilirubin method". These neonates were followed up daily for sign and symptoms of development of jaundice till 5th day of life, because serum bilirubin levels reach its peak between 3rd to 5th day in term healthy neonates.

Significant neonatal hyperbilirubinemia in our study was defined as bilirubin levels ≥ 14 gm/dl as per AAP guideline normogram [5]. The data was entered into the performa in which the gender, gestational age, mode of delivery, anthropometric measurements at birth, cord serum albumin and total and direct bilirubin of the babies were noted. The main outcome of the study was inferred in terms of neonatal hyperbilirubinemia.

Statistic Analysis: The analysis was done using the SPSS Version 21. Statistical data were analysed with t test, chi-square test and ANOVA. Sensitivity, specificity, negative and positive predicative value of the tests was calculated. The cord albumin levels having highest specificity and sensitivity was determined with the Receiver operating characteristics (ROC) curve analysis. The p value with significance of less than 0.05 were considered statistically significant.

Results

In the study a total of 316 neonates were registered. Out of these 182 (57.59%) were male and 134 (42.41%) were female. There was no statistically significant difference in the number of male and female babies. The mean gestational age in our study was 38.65 ± 1.19 weeks and the mean weight was 2.94 ± 0.32 kg. Out of 316 babies 163 (51.58%) babies were born by LSCS and 153 (48.42%) were vaginally delivered, with no significant difference among the babies developing significant hyperbilirubinemia based on the mode of delivery. Oxytocin was used in 171 (54.11%) mothers for either induction or augmentation of labor, no correlation was found between oxytocin use and development of significant hyperbilirubinemia (p>0.05).

Depending on the cord serum albumin levels the babies were divided into 3 groups, Group A (CSA < 2.8 gm/dl), Group B (CSA between 2.8 gm/dl to 3.4gm/dl) and Group C (CSA > 3.4 gm/dl). There was a total of 102 (32.28%) babies in Group A, 166 (52.53%) babies in Group B and 48 (15.19%) babies in Group C.In our study population there was no statistically significant correlation between parity, gender, mode of delivery among CSA groups (p value >0.05). In the present study based on severity of hyperbilirubinemia, neonates were put under two groupsone with bilirubin level ≥ 14mg/dl (significant hyperbilirubinemia) and other with total serum bilirubin level <14mg/dl. Out of total 316 healthy term newborns in our study, 40 newborns (12.66%) had total serum bilirubin >14 mg/dl, while 276 (87.34 %) had total serum bilirubin levels <14 mg/dl and correlation between significant hyperbilirubinemia with CSA groups was measured. The correlation between significant hyperbilirubinemia and cord serum albumin groups was found to be statistically significant (p value <0.0001) which means, “lower serum albumin is associated with higher chances of development of significant neonatal hyperbilirubinemia”(Table 1).

Table1: TSB- Total serum bilirubin, CSA- Cord serum albumin. Relation between cord serum albumin and TSB.

TSB Groups	CSA Group A n (%)	CSA Group B n (%)	CSA Group C n (%)	Total n (%)	P value
TSB < 14 mg/dl	67 (24.28%)	161 (58.33%)	48 (17.39%)	276(100%)	<0.0001
TSB ≥ 14 mg/dl	35 (87.50%)	5 (12.50%)	0 (0%)	40 (100%)	
TOTAL	102 (32.28%)	166 (52.53%)	48 (15.19%)	316(100%)	

Out of 316 neonates enrolled in the study 40 (12.66 %) developed significant hyperbilirubinemia requiring phototherapy and none of the neonate in our study required exchange transfusion.

The sensitivity of CSA level <2.8 g/dl to predict risk of development of neonatal hyperbilirubinemia in our study was 87.50% and specificity was 75.72% while positive predictive value (PPV) was 34.31% and negative predictive value (NPV) was 97.66%. Correlation of CSA level < 2.8 g/dl to predict risk of development of significant neonatal hyperbilirubinemia wasstatistically highly significant (P value = <0.0001).

Discussion

Jaundice is a common and, in most cases, a benign problem in term neonates. However, in some cases it may progress to significant level to cause brain damage. In these cases, the newborn requires early treatment and if the treatment is delayed the newborn may develop kernicterus which leads to long term morbidity. The present study was done to find the possible correlation of cord serum albumin and development of significant hyperbilirubinemia, so that it could be used as

a screening tool to identify at risk neonates. In our study 12.66% of newborns developed significant neonatal hyperbilirubinemia, similar incidence (10-12%) were noted in studies done by Venkatamurthy et al, Rishav Raj et al and Sandeep Kumar et al [7,8,9]. The study group was a uniform representation of both the sex with no statistically significant difference. In present study no significant correlation between gender of neonates and significant hyperbilirubinemia was found. Similar finding was observed by other authors [7,9,10]. However, the studies done by Satrya and Maisels and Kring had found that male babies are at more risk of developing icterus and subsequent intervention for icterus [11,12].

Overall the mean birth weight of our study cohort was 2.94 ± 0.32 kg while mean birth weight in a study done by Suchanda Sahu et al was 3.09 ± 0.16 kg and in a study by Dawarumpudi et al the median weight was 3.2 kg [2,13]. The correlation between birth weight and CSA groups in our study was statistically significant. This shows thatlower the birth weight, lower are the cord serum albumin levels.

There was no statistically significant correlation between mode of delivery and significant neonatal hyperbilirunemia ($p>0.05$). Similar finding was observed in studies done by other authors [2,14,15]. Out of 40 newborn who develops significant hyperbilirubinemia, 35 (87.50%) were in CSA group A and 5 (11.50%) were in CSA group B and none in CSA group C. The correlation between the cord serum albumin level and development of significant hyperbilirubinemia was statistically significant ($p< 0.001$). This means that lesser the cord serum albumin levels more is the chances of newborns developing significant hyperbilirubinemia. While analyzing the diagnostic predictability of cord serum albumin levels among group A (serum albumin ≤ 2.8 mg/dl) for neonatal hyperbilirubinemia in our study, the sensitivity was 87.50% and the specificity was 75.72%. The positive predictive values were 34.31% and the negative predictive value was 97.66%. The same has been depicted in ROC curve shown in figure 1 (AUC = 0.887). In 2011 Suchanda Sahu et al reported 70% neonates developing significant hyperbilirubinemia had cord serum albumin level less than 2.8 mg/dl [2]. In 2014 Venkatmurthy et al observed that cord serum albumin < 2.8 gm/dl had sensitivity of 95% and specificity of 74% in predicting significant hyperbilirubinemia. The positive predictive value was 24.68% and the negative predictive value was 98.97% [7].

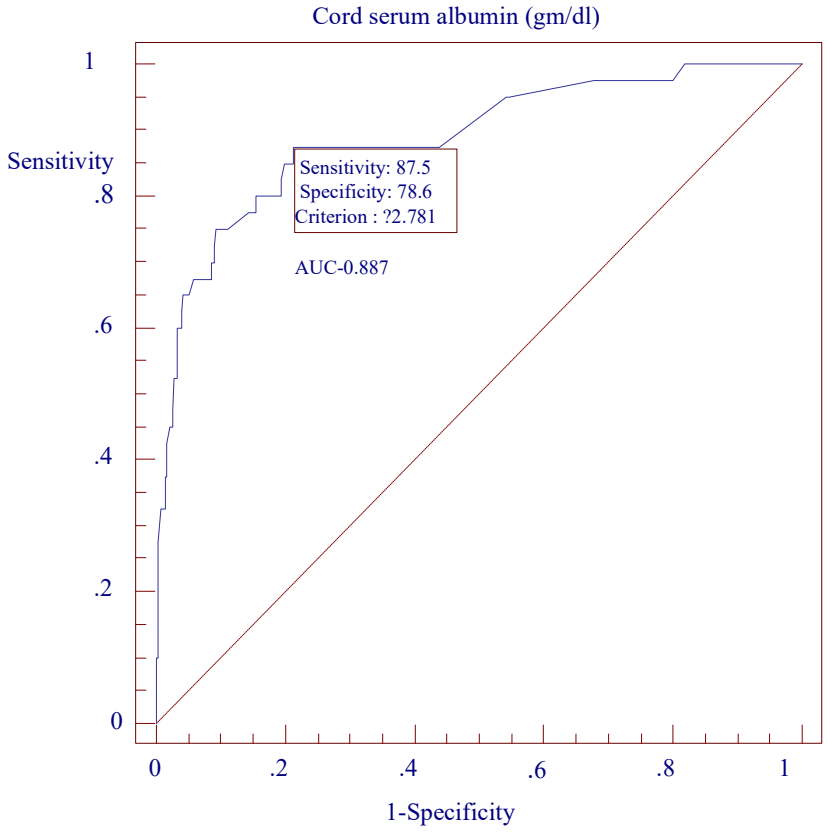

Figure-1: ROC curve. Association between cord serum albumin level and neonatal hyperbilirubinemia

Neeraj et al found that cord serum albumin ≤2.6 gm/dl had sensitivity of 80% and specificity of 86.67% to detect significant hyperbilirubinemia in newborns. The positive predictive value was 40% whereas the negative predictive value was 97.5% [16]. In 2016 Sandeep Kumar et al reported that 90 percent of the neonates who developed significant hyperbilirubinemia were having CSA less than 2.8 gm/dl [9].

Rishav Raj et al found that 95% of neonates developing significant hyperbilirubinemia had cord serum albumin level < 2.8 gm/dl. The sensitivity of cord serum albumin less than 2.8 gm/dl to detect hyperbilirubinemia in newborn was 95%, while specificity was 62.34%. The positive predictive value was 24.68% and the negative predictive value was 98.97% [8].

Shagun Gupta et al observed that cord serum albumin < 2.8 gm/dl had sensitivity of 75.93% and specificity of 68.06% for detecting significant hyperbilirubinemia in newborn. The positive predictive value was 47.2% and the negative predictive value was 88.24%[17].

Aiyappa et al reported the sensitivity of cord albumin to detect hyperbilirubinemia in newborn was determined and found to be 71.8%, while specificity was 65.1%. The positive predictive value was 38.9% and the negative predictive value was 88.2%. The accuracy rate was 67.3 % and the area under the ROC was 0.684[18].

Conclusion

We conclude that cord serum albuminlevel in healthy term neonate is a useful tool in predicting the possibility of neonatal hyperbilirubinemia. Cord serum albumin give additional clue in predicting the possibility of newborn developing significant hyperbilirubinemia later on.

1. Newborns with cord serum albumin level < 2.8 gm/dl are at highrisk of developing significant hyper bilirubinemia, which needs treatment and hence they should be followed closely.
2. Newborns with cord serum albumin level >3.3 gm/dl has very less probability of developing significant hyperbilirubinemia and can be discharged early from hospital.

Contributions

- Dr Gurdeep Singh Dhanjal and Dr Rajesh Kumar Rathi wrote first draft of the manuscript.
- Dr Gurdeep Singh Dhanjal, Dr Rajesh Kumar Rathi, Dr Sonam Agrawal and Dr Savita helped in data collection
- Dr Gurdeep Singh Dhanjal, Dr Rajesh Kumar Rathimade final correction of manuscript before submission.
- All authors approved submission of the manuscript and own responsibility of the manuscript. None of the authors have any conflict of interest.

What this study adds to existing knowledge?

There was no clear cut off value of cord serum albumin level in prediction of significant hyperbilirubinemia. Our study contributes to the fact that a simple cost-effective test like cord serum albumin can go a long way in identifying those newborns who are at risk of developing significant hyperbilirubinemia. In this way we can utilize our limited resources more efficiently.

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