Umbilical Cord Blood Bilirubin Level Measurement in Predicting the Development of Significant Hyperbilirubinemia

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ABSTRACT

Objective: This prospective study was undertaken to identify the newborns at risk for developing significant hyperbilirubinemia using cord blood serum bilirubin levels. Methodology: This was a prospective study with a total of 282 healthy term newborns delivered at MNR Hospital, were included in study with birth weight more than 2,500 grams during one year period from March 2013 to March 2014. Soon after delivery cord blood was sent for serum bilirubin analysis. The data was analyzed using t-test, ROC curve and chi test and was considered statically significant, if value is \( P < 0.05 \). Results: In total 282 children, 51 developed significant hyperbilirubinemia (18.09%). There were no significant differences between the cases who did and who did not develop significant hyperbilirubinemia with respect to various factors that may be associated with the risk of hyperbilirubinemia such as birth weight, type of delivery, gestational age, maternal age, gender, and APGAR value \( P > 0.05 \), while in cord bilirubin level there is highly significant difference \( P < 0.05 \). In our study on the amount of umbilical cord bilirubin cut off point of 2 mg/dl had good sensitivity (94.12), specificity (90.9%), positive predictive value (69.57%) and negative predictive value (98.59%). Conclusion: The present study led to the conclusion that the bilirubin levels that were equal to or greater than 2 mg/100 ml umbilical cord blood can predict significant hyperbilirubinemia with high negative and positive predictive values and high levels of sensitivity and specificity.

KEYWORDS: Cord bilirubin, Hyperbilirubinemia, Kernicterus, Readmission, Specificity and Sensitivity

INTRODUCTION

Jaundice is probably the most common newborn infant problem dealt with on a daily basis by the family practitioner and paediatrician. Nearly all healthy infants have some degree of hyperbilirubinemia and over 60% develop jaundice during their first week of life[1,2]. It occurs in both the physiological and pathological processes in newborns[2]. However, elevated levels of bilirubin, or ‘hyperbilirubinaemia’ treated promptly can usually be resolved in three to four days[3]. Early discharge of healthy term newborns after delivery has become a common practice because of medical and social reasons and economic constraints[4]. In newborns with early hospital discharge the most common reason for rehospitalisation was jaundice[5, 6] and it is risk factor development of kernicterus[7-9] which is a neurological syndrome resulting from deposition of unconjugated (indirect reacting) bilirubin in the basal ganglia and brainstem nuclei[10]. It is difficult to predict which infants are at increased risk for significant and relatively late hyperbilirubinemia, and there is an obvious need to implement follow-up programs or to develop predictive guidelines that will enable the physicians to predict or to identify which of...
the early discharged newborns will develop significant hyperbilirubinemia[5].

Concern regarding early discharge and hyperbilirubinemia in newborns has led to frequent discussions and many controversies[3]. In this study, we aimed to identify the newborns at risk for developing significant hyperbilirubinemia later during the first days of life by measuring serum cord bilirubin levels.

MATERIALS AND METHODS

The present study is a hospital based prospective cohort study to determine cord blood bilirubin levels predictive ability for subsequent hyperbilirubinemia.

Total of 300 healthy term newborns delivered At MNR Medical College and Hospital, Sangareddy were included with birth weight more than 2,500 g. Preterm (<36 weeks), post term (>40 weeks), Rh incompatibility, ABO incompatibility, life threatening congenital anomalies, birth asphyxia and NICU admitted babies were excluded from study. The inclusion of the newborns in the study was done after receiving written consent from their parents or those responsible for them. The study was approved by the Ethics Committee.

The study was done for a period of one year from March 2013 to March 2014. Study group was evaluated by designated protocol.

Soon after delivery 2 ml of umbilical cord blood samples collected and sent for laboratory analysis for cord bilirubin, coombs test. For determination of direct and total bilirubin Jendrassik-Gróf method on photometric systems was used. Then newborn were followed serum bilirubin was estimated when ever clinical suspicion of jaundice. Newborn was defined developed significant hyperbilirubinemia when serum bilirubin was greater than 5 mg/dl in first day, more than 10 mg/dl on second day, and more than 17 mg/dl thereafter.

Sensitivity, specificity, negative and positive predictive value and likely hood ratios of the test were calculated t-test, ROC curve were used when ever useful in statistics. Value $P < 0.05$ was considered as significant.

RESULTS

In this study, out of the 300 infants who were enrolled, 12 were excluded because they had risk factors or had bad general condition. Remaining 282 newborns, 148 (51.3%) males and 134 (48.7%) females. 247 (87.5%) delivered by vaginal and 35 (12.5%) by caesarean.

The predominant blood group among the mothers was the O type, found in 108 cases (38.8%), followed by the A type in 96 cases (34.1%), B type in 70 cases (25%) and AB type in 6 cases (2%). The predominant blood group among the newborns was also the O type, found in 122 babies (43.75%), followed by the A type in 122 babies (43.75%), B type in 51 cases (18.05%) and AB type in 6 cases (2.4%).

There were no significant differences between the cases who did and who did not develop significant hyperbilirubinemia with respect to various factors that may be associated with the risk of hyperbilirubinemia such as birth weight, type of delivery i.e., lower segment cesarean section (LSCS) or normal vaginal delivery (NVD), gestational age, maternal age, gender and APGAR score with value $P > 0.05$, while in cord bilirubin level there is highly significant difference $P < 0.05$ (Table 1).

In total 282 children, 51 developed significant hyperbilirubinemia (18.09%). Hyperbilirubinemia developed in 1.06% of newborns with cord bilirubin <2 mg/dl and in 17.0% of newborns with cord bilirubin >2 mg/dl. The probability that neonates with cord bilirubin >2 mg/dl would later become have hyperbilirubinemia (Positive Predictive Values) was 69.5%. The negative predictive values, the probability that non hyperbilirubinemia given a cord bilirubin lower or equal to 2 mg/dl was 98.59%. If a child becomes hyperbilirubinemic, the probability that the cord bilirubin was higher than 2 mg/dl was 94.12% (Sensitivity). The probability that a cord bilirubin level lower or equal to 2 mg/dl in neonates without hyperbilirubinemia was 90.91% (Specificity). Cord bilirubin levels >2 mg/dl positive likelihood ratio is 10.35 (95% CI 6.85-15.66)
and negative likelihood ratio is 0.06 (95% CI 0.02-0.19).

The results of different amounts of umbilical cord bilirubin and its sensitivity, specificity, positive predictive value and negative predictive value can be observed in Table 2.

### Table 2: Umbilical cord bilirubin cut off values and its sensitivity, specificity, positive predictive value and negative predictive value

<table>
<thead>
<tr>
<th>Cut off value</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive</td>
<td>48</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>False positive</td>
<td>21</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>False negative</td>
<td>3</td>
<td>41</td>
<td>48</td>
</tr>
<tr>
<td>True negative</td>
<td>210</td>
<td>212</td>
<td>215</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>94.12</td>
<td>19.61</td>
<td>5.88</td>
</tr>
<tr>
<td>Specificity</td>
<td>90.91</td>
<td>91.77</td>
<td>93.07</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>69.57</td>
<td>34.48</td>
<td>15.79</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>98.59</td>
<td>83.79</td>
<td>81.75</td>
</tr>
</tbody>
</table>

Receiver operating characteristic (ROC curve) analysis demonstrates that cord blood bilirubin >2.0 mg/dl had the high sensitivity (94.12%) and specificity (90.91%) to predict the newborn that would develop significant hyperbilirubinemia. At this level the negative predictive value was 98.59%. The critical cut off value for the development of hyperbilirubinemia is >2.0 mg/dl [Figure 1].

### DISCUSSION

Jaundice in near-term and term newborns is clinically evident in over 60% of newborns during the first week after birth. Moderate to severe hyperbilirubinemia in the newborn usually peaks between 3 and 7 days of age. This clinical condition is frequently asymptomatic and occurs after hospital discharge. It is significant that the most common cause for readmission during the early neonatal period is hyperbilirubinemia[11,12]. Thus, the recognition, follow-up, and early treatment of jaundice has become more difficult as a result of
earlier discharge from the hospital. However, a complete follow-up is not always possible because of the geography and climate of the area, personal safety, or patient incompliance, and thus, there is a need to identify newborns who are at risk for developing significant hyperbilirubinemia as early as possible. We aimed, in this study, to prospectively determine the critical cord serum bilirubin level to predict significant hyperbilirubinemia in healthy term newborns[5].

In present study a total 51 of 288 (18.09%) were found to have significant hyperbilirubinemia. Similar incidences were reported by Zakia Nahar et al. (15.5%)[13] and Narang et al. (14.5%)[14]. In our study group, there were no significant differences between the cases who did and the cases who did not develop significant hyperbilirubinemia with respect to these factors such as maternal age, gender, delivery route, birth weight, gestational age, and APGAR score that may be associated with the risk of hyperbilirubinemia [Table 1]. In our study on the amount of umbilical cord bilirubin cut off point of 2 mg/dl had good sensitivity (94.12), specificity (90.9%), positive predictive value (69.57%) and negative predictive value (98.59%) [Table 2].

Rosenfeld et al.1986 reported infants with cord bilirubin levels less than 2.0 mg/dl have only a 4% chance of developing hyperbilirubinemia and a 1.4% chance of needing phototherapy. However, if serum cord bilirubin levels are more than 2.0 mg/dl, the infant has a 25% chance of developing subsequent hyperbilirubinemia [15].

Knudsen et al.[16] reported umbilical cord serum bilirubin concentration as a predictor of subsequent jaundice was studied in 291 newborns. It was possible to define subgroups of infants with significantly higher or lower risks of developing jaundice. If cord bilirubin was below 1.17 mg/dl, 2.9% became jaundiced as opposed to 85% if cord bilirubin was above 2.3 mg/dl. Furthermore, 57% of jaundiced infants with cord bilirubin above 2.3 mg/dl required phototherapy, but only 9% if cord bilirubin was 2.3 mg/dl or lower (P<0.003)[16].

Trivedi et al.[17] reported cord serum unconjugated bilirubin level ≥2.0 mg/dl and total cord serum bilirubin level ≥2.5 mg/dl appeared as high risk indicator towards predicting neonatal hyperbilirubinemia.

Bernaldo et al.[3] reported that the unconjugated bilirubin levels in cord blood were indicative of the jaundice severity developed by full-term newborns without complications, up to their third day of life. Levels that were equal to or greater than 2 mg/100 ml indicated a 53% probability of the need for further treatment by phototherapy.

Shaker et al.[18] reported that a critical cut off level of cord bilirubin was 2 mg/dl predicted 71% of the newborns who developed jaundice. However, the cord bilirubin level of <2 mg/dl has not completely exclude the development of significant hyperbilirubinemia. 1.9% of the newborns with cord bilirubin levels of <2 mg/dl have developed hyperbilirubinemia[17].

Knüpfer et al.[19] reported that for the prediction of further need of phototherapy using umbilical cord serum bilirubin cut-off level of 1.76 mg/dl, they found a sensitivity of 90% and a negative predictive value of 99.1%, indicating that all patients with umbilical cord serum bilirubin values below 1.76 mg/dl (443/1100 or 40.2%) were at a very low risk of developing dangerous hyperbilirubinaemia[19].

To target limited health care resources more effectively toward high-risk newborns in the era of early discharge of newborns from hospitals, there is an obvious need to develop practical guidelines to predict which newborns will develop significant hyperbilirubinemia or will require further and close follow-up or intervention. From our particular experience, we conclude that a cord serum bilirubin measurement level of 2 mg/dl will predict nearly all healthy term newborns who will have significant hyperbilirubinemia.

CONCLUSION

The present study led to the conclusion that the bilirubin levels that were equal to or greater than 2 mg/100 ml
umbilical cord blood can predict significant hyperbilirubinemia with high negative and positive predictive values and high levels of sensitivity and specificity and will identify those infants who will require phototherapy later during first days of life. We conclude in short Cord serum bilirubin level is useful in predicting the subsequent jaundice in healthy term infants.

REFERENCES


