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Early Markers for the Prediction of Hyperbilirubinemia in Term Neonates

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Introduction

The incidence of jaundice in neonates is around 65-70% in Western world[1]. and may be higher among newborns of Asian ethnicity. Neonatal jaundice is well known to be associated with increased unconjugated bilirubin concentrations which is caused by the breakdown of red blood cells. Bilirubin damages neurologic tissue and leads to neurologic dysfunction.[2] Bilirubin in itself is not detrimental and exerts a physiological protective effect due to its antioxidant properties. Previous studies have highlighted the relationship between bilirubin and nitric oxide, reactive oxygen/nitrogen species.

The American Academic of Pediatrics (AAP) recommends that newborns discharged within 48 h should have a follow-up visit after 48-72 h for any significant jaundice or other problems.2 In developing countries, follow-up is questionable as mothers do not return because of negligience and distance they need to travel. This may delay the diagnosis of severe neonatal hyperbilirubinemia and thereby causing an increase the incidence of kernicterus. Therefore, several attempts have been made to identify predictors of neonatal hyperbilirubinemia to assist in the early detection of neonates at high risk of severe hyperbilirubinemia. The hour-specific bilirubin nomogram is widely accepted by most clinicians, but has a low sensitivity and may vary by ethnicity. Studies have been performed to assess the ability of cord bilirubin and albumin and first day bilirubin levels as tools for screening of subsequent neonatal hyperbilirubinemia. In the present study we aimed at determining the critical cord serum bilirubin and albumin level that predict significant hyperbilirubinemia in healthy term newborns based on serum bilirubin measurements made within 5 days of life.

Material and Methods

This was a prospective cohort study carried out at a tertiary care centre that included 175 neonates, from January 2015 to January 2016. All neonates were full term (gestational age ranging from 37 to 41 weeks). Newborns with early onset hyperbilirubinemia (bilirubin ≥10 mg/dL before 24 hours of age), maternal ABO incompatibility, G6PD deficiency, cephalohematoma, multiple congenital anomalies, maternal gestational diabetes mellitus, anemia, congenital hypothyroidism, sepsis, cholestasis, RDS and urinary tract infection were excluded. Participants were subjected to detailed history-taking including maternal medical diseases, consanguinity, siblings by hyperbilirubinemia, mode of delivery, Apgar score, oxytocin use, and type of feeding. Thorough physical examination of neonates was

done with assessment of gestational age by new Ballard score and birth weight by growth curves. Immediately following delivery, 3-5 ml of cord venous blood was collected after clamping the umbilical cord with 2 clamps. We tested the collected sample for serum albumin level, serum bilirubin (total and direct) level, hemoglobin concentration and reticulocytic count. Blood groups (ABO, Rh) of newborns and mothers were also determined. Serum bilirubin level were measured on days one, three and five of life for all cases. Significant hyperbilirubinemia was defined as the need of phototherapy or exchange transfusion based on the guidelines of American Academy of Pediatrics.

Results

The population under study included 200 neonates with a mean gestational age of 38.1 (±0.9) weeks and a mean birth weight of 2.7 (±0.3) kg. Of these, 32 neonates (16%) developed significant hyperbilirubinemia (group 1) and 168 neonates (84%) did not develop hyperbilirubinemia (group 2). Among the 32 neonates who developed significant neonatal hyperbilirubinemia, 16 were males and 12 were females; 24 cases delivered by caesarean section and 8 cases received oxytocin for induction of labour. Out othe 168 neonates who did not develop significant neonatal hyperbilirubinemia, 83 were males and 85 were females; 115 cases had delivered by caesarean section and 40 cases had received oxytocin for induction of labour. (Table 1)

Table 1: Case Profile

Parameter	Group 1	Group 2
GA at delivery	37.5weeks	38.3weeks
Birth Weight	2.92kgs	2.87kgs
Gender Male Female	 16 12	 83 85
Caesarean Section	24	115
Oxytocin Augmentation	8	40
APGAR Score 1 min	8	8
APGAR Score 5 min	9	8

Table 2 shows that group 1 infants had statistically significant higher cord reticulocytic count (4.1±1.3%) than those in group 2 (2.4± 0.8%). The difference was highly significant ($p < 0.001$) with a diagnosis of Rh incompatibility in 12% of the cases (4 patients out of 32) and ABO incompatibility in 15.6% of the cases (5 out of 32 patients) in group 1 versus 1.4% and 4.1% respectively in group 2. Cases with significant neonatal hyperbilirubinemia (group 1) had higher cord total bilirubin (2.8±0.2 mg/dl) and lower cord albumin [(2.7±0.3 gm/dl) than those in group 2 (1.6±0.4 mg/dl) and (3.6±0.5 gm/dl) respectively. The difference between the two was statistically significant ($p < 0.001$).

Table 2: Measurement of Laboratory parameters at birth

Laboratory Parameters	Group 1 (n=32)	Group 2 (n=168)	P value
Cord Haemoglobin <16gm% 16-18gm% >18gm% Mean	 8 21 3 16.6±1	 40 115 13 16.1±0.9	0.65
Cord Reticulocytes <3 3-5 >5 Mean	 2 22 8 4.1±1.3	 128 35 5 2.4±0.8	<0.001
Cord Bilirubin(mg%) <1.8 1.8-2.5 >2.5 Mean	 4 10 18 2.8±0.2	 128 36 4 1.6±0.4	<0.001
Cord Albumin <3gm% 3-3.5gm% >3.5gm% Mean	 23 8 1 2.7±0.3	 22 109 37 3.4±0.5	<0.001

Total serum bilirubin levels measured on days 1, 3 and 5 were significantly higher ($P < 0.001$) in group 1[(9.0±1.5mg/dl versus 3.9±1.2mg/dl)], [(16.1±2.6mg/dl versus 6.5±2.5 mg/dl)] and [(14.2± 5.3 mg/dl versus 4.2 ±2.1 mg/dl)] respectively. However, the hemoglobin concentration showed no significant difference between groups.(Table 3)

Table 3: Serum Bilirubin levels at follow up

Total Serum Bilirubin	Group 1	Group 2
Day 1	9.0±1.5	3.9±1.2
Day 3	16.1±2.6	6.5±2.5
Day 5	14.2±5.3	4.2±2.1

Among the neonates that developed significant hyperbilirubinemia, 67.9% had low cord serum albumin<2.8mg/dl, 25% had it ranging between 2.8 and 3.3 mg/dl and only 7% had a level over 3.3 mg/dl. For the prediction of significant neonatal hyperbilirubinemia, a cut off value of cord serum bilirubin of 1.84 mg/dl was chosen on the basis of previous studies. The cord serum bilirubin of 1.84 had a sensitivity of 100%, specificity of 87.1%, positive predictive value of 59.6% and negative predictive value of 100% in the prediction of neonatal hyperbilirubinemia. The optimum cut off value for cord serum albumin as shown by several studies for neonates with significant indirect hyperbilirubinemia was 3 gm/dl with a sensitivity of 85.7% and specificity of 67.3%, negative predictive value of 96.1% and positive predictive value of 33.3%.

Discussion

The need for early prediction of neonatal jaundice is important for identifying babies at risk of neonatal hyperbilirubinemia so as to predict and prevent neurological morbidities caused by bilirubin toxicity. The recent AAP guidelines recommends the use of the total bilirubin concentration/albumin ratio in addition to the TBC for managing healthy jaundiced term and near term newborns; however, it not still widely used by clinicians.

Our study demonstrated a highly significant difference between the cord serum bilirubin levels in the 2 studied groups. They were lower in group who did not develop significant hyperbilirubinemia than those who developed it. A study done by Ipek et al. who found that the mean cord serum bilirubin was lower in babies who developed neonatal hyperbilirubinemia versus those who did not (1.64 _ 0.41 mg/dl versus 2.05 _ 0.9 mg/dl)[3]. Several other studies reported lower mean cord serum bilirubin levels in neonates who developed hyperbilirubinemia. Similar study done by May Ahmed Khairy in Egypt also demonstrated a significant difference between the cord bilirubin level of the neonates who developed hyperbilirubinemia later on(1.4 _ 0.4 mg/dl) versus those who developed it (2.4 _ 0.2 mg/dl).[4] Rajpurohit et al. reported that a cord blood bilirubin cut off value > 2 mg/dl had a sensitivity of 90%, specificity of 53.89%, positive predictive value of 17.8% and negative predictive value of 98% in predicting the risk of neonatal hyperbilirubinemia.[5] Knupfer et al. reported that a cord bilirubin cut off level of 1.76 mg/dl for predicting hyperbilirubinemia had a sensitivity of 70.3% and a negative predictive value of 65.6% . They also concluded that cord blood bilirubin could be used as an early predictor of neonatal jaundice.[6]

Albumin plays an important role in hepatic transportation of bilirubin and its clearance. Low serum albumin level decreases bilirubin clearance and thereby increases significant hyperbilirubinemia.[7] The ability of cord albumin for predicting neonatal jaundice was assessed in the current study. Cord serum albumin level were significantly higher in neonates who did not develop neonatal hyperbilirubinemia in comparison to those who did. Burtis et al. [8] found the cut off for cord serum albumin in term babies was 2.8 gm/dl. Reshad et al.[9] found that in the term group, 19 (61.2%) newborns with cord serum albumin <2.8 g/dl developed neonatal hyperbilirubinemia. May Ahmed Khairy reported the lower normal limit of cord albumin to be <3gm% for prediction of neonatal hyperbilirubinemia. Dwarampudi and Ramakrishna suggested that cord albumin levels (>2.8 gm/dl) were probably safe to discharge a neonate in respect to the risk of development of neonatal hyperbilirubinemia.[10] Moreover, similar results were reported by several researchers who found that cases with low cord albumin <2.8 gm/dl developed more significant hyperbilirubinemia requiring phototherapy and exchange transfusion.

Conclusion

We found a significant correlation between cord blood bilirubin and albumin levels and development of neonatal hyperbilirubinemia.

Early prediction will enable the pediatrician to identify the high risk babies and and subsequent timely intervention could prevent the complications of neonatal hyperbilirubinemia. The labour room staff could be trained and instructed by the attending pediatrician for sample collection. Incorporation of this technique in the routine practice would help bring down the neonatal morbidity and mortality.

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