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Correlation of Cord Blood Bilirubin with Significant Neonatal Hyperbilirubinemia in Term Newborns

KEYWORDS: Neonatal Hyperbilirubinemia,Neonate.

Dr PM Khare
Department of Pediatrics, Dr D Y Patil medical college, and Research Institute, kolhapur.

Dr Pradeep singh
Department of Pediatrics, Dr D Y Patil medical college, and Research Institute, kolhapur

ABSTRACT *Jaundice is one of the commonest problems that can occur in a newborn. It is important to identify babies at risk of hyperbilirubinemia, as it can cause acute bilirubin encephalopathy and kernicterus which have a high mortality and significant morbidity with long term squeal.*

AIMS & objective- *To assess the predictive value of the cord blood bilirubin as an early predictor of neonatal hyperbilirubinemia in order to implement early treatment and there by minimize the risk of Bilirubin dependent brain damage. All the healthy newborns (37weeks-41weeks), delivered at this hospital fulfilling the inclusion and exclusion criteria were enrolled in the study. Gestational age was assessed by New Ballard score. METHODOLOGY- Cord blood bilirubin, Baby Blood group and Direct Coombs test were estimated. Repeat Serum Bilirubin estimation was done at 72 hours of age.*

RESULT- *The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software. A statistically significant association of neonatal hyperbilirubinemia and cord bilirubin levels was found (p=0.003). An increase in incidence of hyperbilirubinemia with increase in cord bilirubin levels was found.*

CONCLUSION-*i t can be concluded that cord blood bilirubin levels might have a high efficacy in early treatment of hyperbilirubinemia and minimization of risk of bilirubin dependent brain damage.*

Jaundice is one of the commonest problems that can occur in a newborn. During the first week of life all newborns have increased bilirubin levels by adult standards, with approximately 60% of term babies and 85% of preterm babies having visible jaundice. This physiological rise in bilirubin causes indirect hyperbilirubinemia after 24 hours of birth, rises progressively with age and resolves gradually with no intervention in majority of cases. A small percentage may however require phototherapy or exchange transfusion when the bilirubin levels exceed the normal range. It is important to identify babies at risk of hyperbilirubinemia, as it can cause acute bilirubin encephalopathy and

Kernicterus which have a high mortality and significant morbidity with long term sequalae.

Bilirubin is produced from heme released from destruction of senescent RBCs in the reticuloendothelial system. It is transported to liver by binding to albumin. It is conjugated in the liver and excreted in stool and urine. During intrauterine life, the placenta removes bilirubin from the fetus and after birth, this function is taken over by the liver. However, it may take some time for the liver to be able to do this efficiently.

Newborns produce bilirubin at a rate of approximately 6 to 8 mg per kg per day. This is more than twice the production rate in adults, primarily because of relative polycythemia and increased red blood cell turnover in neonates[1].

This exceeds the conjugating capacity of the neonatal liver leading to indirect hyperbilirubinemia . Bilirubin binding to albumin is influenced by acidosis, hypoalbuminemia, lower gestational age, postnatal age (age <3 days) and interference by drugs such as sulfa and some cephalosporins .Indirect bilirubin can cross the blood brain barrier and cause acute encephalopathy. Acute bilirubin encephalopathy can manifest as hypotonia, high pitched cry, retrocollis and seizures.

Bilirubin production typically declines to the adult level within 10 to 14 days after birth[2].However; some neonates can have exaggerated physiological hyperbilirubinemia requiring phototherapy and exchange transfusion. Breast milk jaundice and breast feeding jaundice can exacerbate the hyperbilirubinemia but require no treatment.

Risk factors for elevated indirect bilirubin include maternal age, race, maternal diabetes, prematurity ,drugs like vitamin K etc , altitude, polycythemia, male sex, trisomy 21, cutaneous bruising, blood extravasation (cephalohematoma), congenital hypothyroidism, birth asphyxia, Rh isoimmunisation, ABO incompatibility, oxytocin induction, breastfeeding, weight loss/dehydration, delayed bowel movement and a family history of a sibling who had physiological jaundice.

DISCUSSION

The present study was carried out to evaluate the role of bilirubin levels in cord blood in predicting neonatal hyperbilirubinemia in full-term newborns. A total of 100 full-term newborns admitted to Department of Paediatrics of Dr D Y Patil Hospital & Research institute Kolhapur were enrolled in the study.

On evaluating the maternal profile a total of 15 (15%) mothers were aged ≤20 years of age whereas a total of 4 (4%) were above 30 years of age. Both advancing age as well as pregnancies at younger age have been reported to be associated with risk of NICU admission[53,54,55]. In India, prevalence of teenage pregnancies has been reported to be varying from 8.7% to 24% from various set ups[56,57,58]. On the other hand prevalence of late pregnancy

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(in fourth decade or above) is relatively lower (6.5%) in India[59]. Trends seen in Indian subcontinent reveal that rates of child bearing is maximum between 20 to 30 years of age and prevalence of pregnancy beyond the age of 30 years is relatively lower[60,61]. The findings of present study also endorsed maximum proportion of women in 20-30 years age group and pregnancy beyond 30 years to be minimum.

In present study, almost half the mothers (54%) were multipara, and a total of 28 (28%) had pregnancy induced hypertension. Relationship between parity and NICU admission has been viewed variedly. In a study by Başer *et al.* (2013)[62], for advancing age pregnancy (≥40 years) the NICU admission rate was almost twice in nullipara (15.2%) as compared to multipara (5.7%) whereas in mothers aged 20-30 years the rate of NICU admission was lower in nullipara (6.9%) as compared to multipara (8.9%). Although, none of the mothers in present study were aged ≥40 years and as such proportional distribution of multipara to nullipara in present study (54/46; 1.17:1) is similar to that reported in the cited study (1.29:1)[62]. Pregnancy induced hypertension is a known risk factor for NICU admission[63,64]

With respect to gender of newborn, majority of newborns included in the study were males (56%). The higher proportion of males admitted to NICU could be attributed to a higher risk and susceptibility of morbid conditions requiring NICU admission in males. In a study by Gowda *et al.* (2014)[65] male gender was found to be significantly associated with a higher risk of NICU admission. There is plenty of evidence available that neonatal conditions responsible for NICU admission such as neonatal sepsis are more common in males as compared to females[66,67,68,69,70].

In present study we observed maximum proportion of our subjects in the weight range 2500-3000 gms (66%). Only 34 (34%) subjects were above 3000 gms of weight. In a study by Mathai *et al.* (1996), the 10th to 90th centile birth weights of babies born in a tertiary care hospital were observed to be falling in the same range. They had shown the birth weights of female babies to be lighter than those of males in both first-born and later-born groups. However, in present study we did not distinguish between these parameters. In our study only 34% of babies born in this category of weight were above >3000 gms of weight whereas in the study of Mathai *et al.* (1996), the 90th centile birth weights were above 3500 gms. This difference might be because of probable difference in socioeconomic and demographic profile.

All the babies were born at term as per the inclusion criteria, however, a sizeable proportion of neonates (47%) were post-dated pregnancies (40 weeks and above)[72]. None of the neonates were prolonged (>42 weeks). Prolonged gestation complicates 5% to 10% of all pregnancies and confers increased risk to both the fetus and mother[73,74,75] and this could be one of the reasons for a high percentage of neonates in NICU with a gestational age above 40 weeks.

Majority of babies were born through normal vaginal delivery. Although both elective as well as emergency caesarean sections have been shown to be significant predictors of NICU admission[76,77] yet the lower proportion of neonates with caesarean delivery could be attributed to a strict exclusion criteria used in present study.

Keeping in line with the ABO profile matching, no ABO or Rh incompatibility of mother and child was seen. This was essential as ABO and Rh incompatibility is a known risk factor for neonatal hyperbilirubinemia[78,79,80]. Thus, the confounding role of ABO and Rh compatibility was ruled out.

During the study, an interesting finding was made, it was observed that proportion of neonates born within 37-39 wks 6 days predominantly weighed ≤3 kg whereas those born at gestational age 40-42 weeks predominated those weighing >3 kg.

In present study, majority of subjects had baseline cord bilirubin levels in the range of 1.0 to 1.99 mg/dl (58%). Only a total of 14% had cord bilirubin levels <1 mg/dl. A total of 22% subjects had cord bilirubin levels in the range of 2-2.49 mg/dl while 6% had cord bilirubin levels >2.5 mg/dl. According to Appleton and Lange's Outline Review of Clinical Chemistry, the cord blood levels <2.0 mg/dl are considered to be in normal range (Appleton & Lange, 2001)[81]. Thus in present study we had a total of 26% cases had cord blood levels above the prescribed reference range. The proportion of neonates with cord blood bilirubin level >2.5 mg/dl was reported to be 13.1% in a study by Nahar *et al.* (2009)[41] which is much higher than that reported in present study (6%). However, proportion of neonates with cord blood level >2 mg/dl as observed in present study (26%) was similar to that reported by Taksande *et al.* (2005)[82]. Contrary to present study where maximum value for cord blood bilirubin was recorded as 3.24 mg/dl, Chen and Ling (1994) found 12/80 (15.0%) of their neonates to have cord blood bilirubin level above 4.0 mg/dl. However, the difference between present study and that of Chen and Ling's study[83] was that their study was carried out in ABO incompatible neonates whereas in present study, ABO incompatibility was ruled out.

In present study, majority of newborns had direct bilirubin levels were 0.51-1.00 mg/dl (68%) followed by that of 0.1-0.5 mg/dl (31%). Mean direct cord bilirubin levels were 0.66±0.22 mg/dl. Most of the studies in past have reported only cord blood total bilirubin levels, only a few studies have reported cord blood direct bilirubin levels. In one such study, Farhat *et al.* (2013)[44] reported mean cord blood direct bilirubins to be 0.3 mg/dl which is much lower than that observed in present study. One of the reasons for this could be the difference in study population. The present study was carried out among neonates admitted to NICU whereas the study of Farhat *et al.* (2013)[44] did not specifically enrol the NICU neonates.

In present study, no significant association between birth weight and cord blood and 72-hr blood bilirubin levels was seen. Except for birth weight >3.5 kg, for all birth weight categories, a significant increase in serum bilirubin levels as compared to cord blood bilirubin levels was observed. Contrary to findings of present study, a significant association between cord blood bilirubin levels and birth weight was observed by Taksande *et al.* (2005)[82] but no significant association between birth weight and 72-hr blood bilirubin levels was observed by them – much like the finding in present study. The difference between two studies is that the present study included only full term normal birth weight babies (≥2.5 kg), however, Taksande *et al.* (2005)[82] included low birth weight babies too. In another study, Zeitoun *et al.* (2013)[84] who compared cord blood and transcutaneous bilirubin levels between full-term and preterm neonates found a significant difference in birth weight of two groups but did not find a significant difference between two groups for cord blood or transcutaneous bilirubin levels upto 9th day after birth. However, in a

study by Sahu *et al.* (2011)[85] just opposite trends were obtained. They observed that the birth weight of babies with cord blood levels of higher order of serum bilirubin were higher as compared to those having lower cord blood serum bilirubin.

Most of the previous studies did not find a significant association between birth weight and serum bilirubin levels[50,86,87]. It would be pertinent to mention here that in present study no low birth weight or preterm deliveries were included. Hence, the findings in present study should be interpreted in context of full-term normal weight deliveries only.

In present study, no significant association between neonatal serum bilirubin levels and gender of baby was observed. Similar to findings of present study, In another study Agarwal *et al.* (2007)[87] too did not find any association between gender and occurrence of neonatal hyperbilirubinemia. Farhat *et al.* (2013)[44] and Chary *et al.* (2014)[50] also made observations to similar effect. Contrary to our results, Trivedi *et al.* (2013)[47] found male gender to be at higher risk of developing hyperbilirubinemia. However, they did not provide any explanation for this association and hence the gender association in their study could be considered to be incidental only.

In present study, no significant association between cord blood bilirubin levels and neonatal serum bilirubin levels was observed (p=0.477) when categorical comparisons were made, however, when cord blood and serum bilirubin levels of normal and hyperbilirubinemic neonates were compared then a significant difference was observed between the two (p<0.001). Correlation between cord blood bilirubin and serum bilirubin levels was significant tending towards a mild positive (r=0.3) and significant relationship (p=0.003).

The absence of a significant association for categorical associations could be attributed to large number of cord blood bilirubin categories (6 categories) and fewer number of cases in some specific categories (CB Bilirubin 2.50 mg/dl and above). Thus indicating a need for realignment of categories. Table D1 below shows a realigned exploration of this relationship: as its well know that most of the people are unaware of neonatal jaundice and in periphery health care centres discharge the mother in less than 48hrs,due to economical constraints and limited pt's and bed ratio , although they were advised for follow up on 3rd day of life. But due to lake of awareness they don't bring the new born to health care centre, and more over in rural area mothers are kept in dark room , so till the time they notice yellowish discoloration it's too late to diagnose early neonatal hyperbilirubinemia, so our study is to yield such screening tool by which we can predict the 3rd day neoanatal hyperbilirubinemia ,at periphery also one can do simple cord blood investigation and can predict which baby will develop hyperbilirubinemia for timely treatment, And can minimize the risk of bilirubin dependent brain damage, by initiation of early simple treatment like phototherapy.

SUMMARY AND CONCLUSION

On the basis of observations made in present study, the following conclusions have been drawn:

The present study included newborns of mothers aged 18-35 years with a mean age of 24.79±3.54 years, with majority being multipara (54%) and a sizeable proportion of them having PIH (28%).

The male to female ratio of neonates enrolled in the study was 1.27:1.

All the neonates were full term, normal weight (≥2.5 kg) babies born at 37 to 40 weeks of gestation. Majority are born by normal vaginal deliveries (64%). No ABO incompatibility was seen. All mothers and neonates were Rh positive. Blood group O+ was most common (31%) while A+ was least common (19%).

Cord blood bilirubin levels ranged from 0.91-3.24 mg/dl with a mean value of 1.69±0.51. A total of 28% neonates had cord blood bilirubin levels ≥2 mg/dl.

Direct cord blood bilirubin levels ranged from 0.20-1.1 mg/dl with a mean value of 0.66±0.22 mg/dl. Majority (68%) had cord blood direct bilirubin levels within 0.51-1.0 mg/dl range. Only 1 (1%) had cord blood direct bilirubin level above 1 mg/dl.

The correlation between total and direct cord blood bilirubin levels was weak and not significant statistically (r=0.010; p=0.921).

No significant association between birth weight and cord blood or neonatal serum bilirubin levels was observed.

No significant association between cord blood bilirubin levels and gender was observed. Similarly, no significant association between neonatal hyperbilirubinemia and gender was observed.

No significant association between birth weight and neonatal hyperbilirubinemia was observed.

A significant association between cord blood levels and neonatal serum bilirubin levels was observed (Table D1).

Mean cord blood as well as neonatal serum bilirubin levels of neonates born with and without hyperbilirubinemia was observed.

A positive and significant correlation between cord blood bilirubin and serum bilirubin levels was observed.

Mean cord blood bilirubin levels showed a significant incremental trend with increasing neonatal serum bilirubin levels, however, cord blood direct bilirubin levels did not show such association.

No significant association of ABO group, parity, gestational age category, mode of delivery and cord blood and serum bilirubin levels was observed.

Phototherapy was initiated in 24 neonates. All the neonates responded well and no adverse outcome was reported.

On receiver operator curve analysis a cut-off value cord blood bilirubin level ≥1.875 showed a sensitivity, specificity, positive predictive value and negative predicative value of 76.8%, 61.3%, 81.5% and 54.3% respectively.

For fixed interval cord blood bilirubin levels the sensitivity, specificity, positive predictive value and negative predictive values at cut-off values 0.5 mg/dl (100%, 20.3%, 100% and 36%), 1.0 mg/dl (87.1%, 52.2%, 90% and 45%), 2 mg/dl (41.9%, 78.3%, 75% and 46.4%) and 2.5 mg/dl (9.7%, 95.7%, 70.2% and 50%) respectively.

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The findings of present study indicated that cord blood bilirubin levels had a significant association with 72-hr neonatal serum bilirubin levels, however, the predictive accuracy of different cut-off values is still to be explored extensively. Considering this relationship and a good response to phototherapy, it can be concluded that cord blood bilirubin levels might have a high efficacy in early treatment of hyperbilirubinemia and minimization of risk of bilirubin dependent brain damage