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CORD BLOOD ALBUMIN AND BILIRUBIN LEVELS AS PREDICTORS IN NEONATAL HYPERBILIRUBINEMIA

GOWTHAMI SANDHYA DWARAMPUDI[1*] AND N. RAMAKRISHNA[2]

[1]Senior Resident, Department of Biochemistry, Rangaraya Medical College, Kakinada.*
[2]Former professor, Department of Biochemistry, Andhra Medical College, Vishakhapatnam.

ABSTRACT

Neonatal hyperbilirubinemia resulting in clinical jaundice is a common problem during the first weeks of neonates life. Most common cause of hyperbilirubinemia in neonates is physiological hyperbilirubinemia. Although physiological hyperbilirubinemia is 100% curable;Fallow up and the early treatment has become difficult due to early discharge from the hospital. Physiological hyperbilirubinemia results from immature liver cell having very low uridine diphospho glucuronosyl transferase activity compared to mature hepatocyte, low concentration of Bilirubin binding ligand Albumin, and higher volume of short life erythrocytes in the circulation. Studies strongly argues for the primacy of bilirubin in the etiology of kernicterus. present study: estimation of neonatal cord blood albumin and bilirubin levels and assessing their reliability with the third day neonatal peripheral venous sample bilirubin levels. To assess the reliability of cord blood albumin and bilirubin levels in early prediction of Hyperbilirubinemia in neonates. Present study was conducted on 70 neonates (term & preterm) whose cord blood was estimated for albumin and bilirubin levels by dye binding method and modified dimethylsulfoxide methods respectively. Incidence of Hyperbilirubinemia is confirmed by estimating peripheral venous blood bilirubin levels by DMSO method on day third of the neonate . Frequency of hyperbilirubinemia in neonates in our center at term is 52 % and in pre-tem is 70% [10,11]. Cord blood albumin level of < 2.8 gm/dl has a sensitivity of 74% and specificity of 88%[9,13]and Cord bilirubin level >2mg/dl has 70% sensitivity and 90%specificity [7, 9], in predicting the risk of neonatal hyperbilirubinemia. Present study supports that Cord blood albumin and bilirubin levels are reliable in predicting development of hyperbilirubinemia. This study also supports gestational age has impact in developing hyperbilirubinemia. By early detection of hyperbilirubinemia treatment option will be simple phototherapy which prevent neonate from having unnecessary transfusions. Recommendations: Hence it is recommended to include estimation of cord blood albumin and bilirubin levels as a routine investigation for the neonates to prevent the dangerous consequences of neonatal hyperbilirubinemia like kernicterus. ABREVATIONs: CSA: Cord serum Albumin, TB: Total bilirubin, UB: Un conjugated bilirubin.

KEYWORDS: **Albumin, Bilirubin, Cord blood, Hyperbilirubinemia, Neonate.**

GOWTHAMI SANDHYA DWARAMPUDI
Senior Resident, Department of Biochemistry,
Rangaraya Medical College, Kakinada.

***Corresponding author**

INTRODUCTION

Health is defined as a state of complete physical, mental, and social well being and not merely an absence of disease or immunity. Health is a fundamental human right[1]. Infant mortality rate is one of the most universally accepted indicator of health status[1]. Infant mortality rate is often used as an indicator of the level of health in a country. The ultimate aim should be to benefit the maximum number of new born babies with improved survival and reduced mortality.Though babies with ABO / Rh incompatibility are at high risk for developing subsequent hyperbilirubinemia, many a times it is physiological. Physiological hyperbilirubinemia results from immature liver cell having very low uridine diphospho glucuronosyl transferase activity compared to mature hepatocyte, low concentration of Bilirubin binding ligand Albumin, and higher volume of short life erythrocytes in the circulation. Physiological jaundice arises as a "normal" response to the baby's limited ability to excrete bilirubin in the first days of life. Every newborn develops an unconjugated hyperbilirubinemia due to increased level of unconjugated Bilirubin above 1.0mg/dl. Clinical jaundice is seen in 60-70% of term and about 80% of preterm newborns[2]. The potential risk of developing unconjugated bilirubin encephalopathy or even kernicterus is higher in babies with elevated unconjugated bilirubin level. The sequel could be serious as patients may develop cerebral palsy, sensoneural deafness and mental retardation[3]. Treatment of severe neonatal jaundice by exchange transfusion is costly, time consuming and associated with complications. Early treatment with phototherapy is effective, simple and cheap. This technology is appropriate in treating neonatal jaundice[4]. The pathogenesis of the basal ganglia lesions has been actively debated in the literature throughout the twentieth century and is likely to continue to be debated well into the twenty-first century. Several authors suggested that bacterial infection injured the cells sufficiently to permit entry of unconjugated bilirubin along with lipid, while others implicated toxins, shock, bile salts and even trauma [5] It is fair to say that to this very day, we do not yet know the true biochemical pathology of kernicterus, nor can we attribute to bilirubin alone the responsibility. Yet, the occurrence of kernicterus in the Gunn rat and especially in the genetically identical Crigler-Najjar Syndrome[6] described in 1951 there are no apparent defects other than severe hyperbilirubinemia, strongly argues for the primacy of bilirubin in the etiology of kernicterus. widely accepted contributory role of defective albumin binding in the pathogenesis of kernicterus was elaborated by Odell in 1959. Albumin binding of bilirubin, the impetus for these studies came, of course, from the elegant, controlled clinical trial of William Silverman and colleagues, reported in 1956, showing an increased incidence of kernicterus in those premature infants assigned at random to an antibacterial regimen containing sulfisoxazole. The effect of light on jaundice in neonates, and the ability of light to decrease serum bilirubin levels, was first described by Cremer et al in 1958. This observation led to the development of light sources for use in the treatment of infants with hyperbilirubinemia, a treatment now referred to as phototherapy. Bilirubin is a potentially toxic product of heme catabolism that is normally cleared from plasma by the liver, conjugated with glucuronic acid and excreted into bile. Newborn infants with low levels of bilirubin glucuronosyl transferase and people with a severe genetic deficiency of this enzyme are at risk for developing bilirubin toxicity, which occurs when bilirubin levels in cells become sufficiently elevated to interfere with normal cellular functions. Albumin is synthesized by liver and it helps in transport of unconjugated bilirubin. Plasma albumin limits the toxicity of bilirubin by reducing the unbound bilirubin concentration and thereby competing with tissues for bilirubin binding. Extremely avid binding to albumin may be detrimental, however, because it limits the rate of hepatic removal of unconjugated bilirubin from the plasma. Thus, the affinity of albumin for unconjugated bilirubin may reflect a compromise between the need to prevent

excessive binding to tissues and the need for efficient hepatic elimination. There is paucity of reports on serum albumin or cord blood albumin levels as a predictor of hyperunconjugated bilirubinemia.[7,8,9]

METHODS AND MATERIALS

After taking KGH'S ethical committee consent , Study was done from January2014 to June 2014 for a period of 6 months which include 70 single live term and preterm born neonates delivered in Govt. Victoria hospital for women and children and King George hospital Visakhapatnam will form cohort of this prospective study.Samples were taken, After taking the consent of the baby's guardian,. After the cord has been detached from the newborn, cord blood collected through umbilical vein into 5ml syringe. Blood sample collected was stored away from light. The sample was refrigerated between 2 -8 degree C till serum total and direct bilirubin estimation is done. Serum Bilirubin estimation was done within 12 hours of collection of sample .On the third day, again with the consent of the guardian, peripheral venous blood was collected for estimation of third day serum bilirubin. Serum albumin and serum bilirubin levels were estimated by BCG and DMSO colorimetric methods respectively.

RESULTS

Study includes 70 term and preterm born neonates, delivered in Govt. Victoria hospital for women and children and King George hospital Visakhapatnam , selection of neonates done based on the criteria who otherwise have no any other abnormality or signs of having complicated jaundice or any other known diseases will form cohort of this prospective study. The study results were analyzed using appropriate statistical methods.

TABLE 1
Demographic Distribution of Study Group

	Controls	Cases	PERCENTAGE (%)
TERM NEONATES	24	22	52
PRE TERM NEONATES	8	16	48
TOTAL	32	38	100

TABLE 2
Cord Albumin (gm/dl), Cord Bilirubin (mg/dl) and 3rd Day Serum Total Bilirubin (mg/dl) in Term Neonates

	TERM NEONATES		
	CONTROLS (24) Mean ± SD	CASES (22) Mean ± SD	p value
CSTB mg/dl	1.388± 0.548	2.571± 1.140	<0.01
CS albumin gm/dl	3.574± 0.44	2.355± 0.492	<0.033
serum TB levels on 3rd day	5.86± 0.929	10.45± 1.679	<0.01

FIGURE 1
Bar Diagram Showing Comparison between Cord Albumin (gm/dl), Cord Bilirubin (mg/dl) and 3rd Day Serum Bilirubin (mg/dl) In Term Neonates

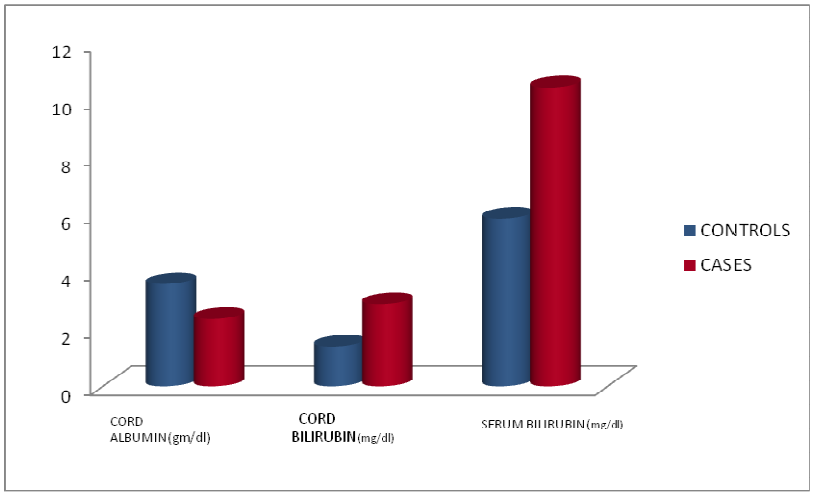

TABLE 3
Cord Albumin (gm/dl), Cord Bilirubin (mg/dl) and 3rd Day Serum Bilirubin (mg/dl) in Preterm Neonates

	PRETERM NEONATES		p value
	CONTROLS Mean ± SD	CASES Mean ± SD	
CSTB mg/dl	1.3± 0.19	2.806± 0.891	<0.04
CS albumin gm/dl	3.1± 0.712	2.119± 0.583	<0.015
Serum TB levels on 3rd day	10.825± 1.165	16.338± 1.134	<0.01

FIGURE 2
Bar Diagram Showing Comparison Between Cord Albumin (gm/dl), Cord Bilirubin (mg/dl) and 3rd Day Serum Bilirubin (mg/dl) in Term Neonates

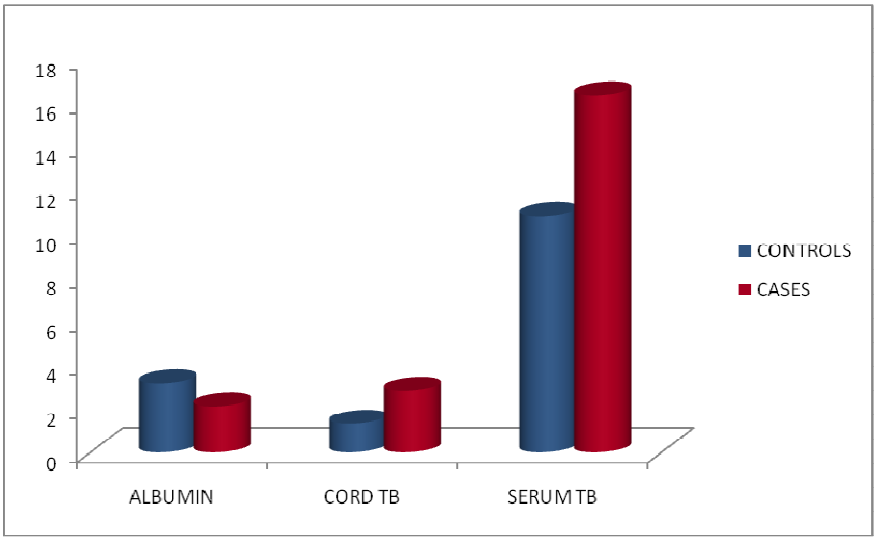

TABLE 4
ALBUMIN TEST RESULTS

TEST RESULT	DISEASED	NOT DISEASED	TOTAL
(+VE)	26	4	30
(-VE)	8	32	40
TOTAL	34	36	70

Sensitivity = 74 %
Specificity = 88%
Ppv = 86%
Npv = 78%.

TABLE 5
BILIRUBIN TEST RESULTS

TEST RESULT	DISEASED	NOT DISEASED	TOTAL
(+VE)	18	4	22
(-VE)	8	40	48
TOTAL	26	44	70

Sensitivity = 70 %
Specificity = 89.4%
Ppv = 73%
Npv = 81%

DISCUSSION

Present study consists of two groups. Group 1 represents term neonates, in which neonates having cord blood bilirubin (< 2mg/dl) and did not develop hyperbilirubinemia (when serum bilirubin on 3rd day 4-8 mg/dl) are considered as controls, irrespective of cord bilirubin levels one who developed hyperbilirubinemia (>8mg/dl) by day three are considered as cases. As serum bilirubin values are varied from one laboratory to other here the reference values are considered from our hospital.[9] Group 2 consists of preterm neonates ,in which neonates having cord blood bilirubin (< 2mg/dl) and did not develop hyperbilirubinemia (when serum bilirubin on third day it is 10-14mg/dl) are considered as controls, irrespective of cord bilirubin levels one who develops hyperbilirubinemia on day three (>14mg/dl) are considered as cases.Comparing Group 1 (term) and Group 2 (preterm) distribution showing in group1, 52.17% neonates are under cases where as in pre-tem 70% are under case group .Study shows that gestational age has impact in developing hyperbilirubinemia. Chi-square test is done between two groups and result is statistically significant (p value 0.04). Similar observation was made by Singhal et al-1992[11,] and Narang etal - 1997 [11] on the other hand some researchers did not find any significant effect of gestational age.In term neonates cord albumin mean of controls in group 1 is 3.574 ± 0.44 gm /dl and of cases is 2.355±0.492gm/dl. In pre term neonates cord albumin mean of controls in group 1 is 3.1 ± 0.712 gm /dl and of cases is 2.119 ± 0.532 gm/dl, cord albumin levels are decreased in both term and preterm neonates cases when compared with controls which is statistically significant (p value < 0.04). Similar results were seen in Suchanda sahu et al -2011 [7]and Trivedi et al-2013.[10] Were as cord bilirubin controls in Group 1 is 1.388±0.548mg/dl (normal <2 mg/dl) and of cases is 2.571±1.140. In pre term controls in group 2 is 1.3±0.19mg/dl (normal <2 mg/dl) and of cases is 2.806 ±0.89 and levels are increased in cases when compared with controls in and it is statistically significant (p value < 0.011)[12] in both term and pre term neonates similar results were seen in Zakia Nahar,Md .Shahidullah,Abdul Mannan Et al-2009[13], Trivedi et al 2013.[9] 3 rd day serum bilirubin mean in Group 1(term) controls is 5.86±0.929 and in cases it is 10.45±1.693, in Group 2 (pre term) controls it is 10.825±1.165

and in cases it is 16.338 ± 1.134 which is statistically significant (p value <0.01) in both. Similar results were shown by Trivedi et al 2013 [9] and Zakia Nahar, Md.Shahidullah, Abdul Mannan et al-2009.Out of 70 neonates who has cord albumin levels <2.8 mg/dl are 30 of which who developed hyperblirubinemia by day three are 26 and the remaining 4 does not develop any hyperbilirubinemia ,in remaining 40 neonates who has cord albumin levels >2.8mg/dl,8 developed hyperbilirubinemia by day three remaining 32 did not develop any significant hyperbilirubinemia. By using appropriate statistical formulas we estimated Cord albumin test result is 74% sensitive and 88% specific has 86% ppv and 78% npv in prediction of hyperbilirubinemia by third day. So adequate cord albumin levels(> 2.8 gm/dl) are probably safe to discharge a neonate with respect to suspicion of development of hyperbilirubinemia. Suchenda sahu at el[7] and trivedi at al[10] shows similar results. Whereas Out of 70 neonates, 22 are having cord blood bilirubin levels more than 2mg/dl, of which 18 developed hyperbilirubinemia by day three and the remaining 4 had normal bilirubin levels by day three , out of 48 neonates whose cord blood bilirubin levels are in normal range 8 developed significant hyperbilirubinemia and remaining 40 did not develop any raised bilirubin levels. By using appropriate statistical formula Cord bilirubin test result is 70% sensitive and 90% specific with ppv 73% and npv 81%. Hence present study supports neonates having cord bilirubin level less than 2mg/dl are in safe zone with respect to development of subsequent hyperbilirubinemia .Similar results were shown by zakianahar ,mdsahahidullah,abdul mannan et al-2009[13] Thus cord serum albumin and bilirubin levels appears to be risk indicators in predicting neonatal hyperbilirubinemia. Similar observations were made by Trivedi et al 2013 .[9] On the other hand Rostami et al [14] on their study did not identify any significant association between cord bilirubin levels and development of hyperbilirubinemia on third day of neonates. They concluded that cord serum bilirubin cannot identify subsequent hyperbilirubinemia. Present study results are not in agreement with Rostami et al.

Limitations

Study was conducted on a small group. In view of early discharge of the babies delivered vaginally, increased representation of babies extracted from caesarean section are taken.

CONCLUSION

present study shows that gestational age has impact in developing hyperbilirubinemia[10,11.]as 52.173% term neonates falls under cases where as in pre-tem 70% are under case group i.e who develops hyperbilirubinemia .Cord blood bilirubin level of ≥ 2gm/dl has a sensitivity of 70% and specificity of 89% in predicting the risk of neonatal hyperbilirubinemia. [9,13] Cord blood albumin level of < 2.8 gm/dl has a sensitivity of 74% and specificity of 88% in predicting the risk of neonatal hyperbilirubinemia. [7,9] Thus by estimating the levels of cs albumin and bilirubin in newborn helps in predicting the risk of developing hyperbilirubinemia in neonates. Thus we recommend to include cord blood albumin and bilirubin levels estimation as a routine investigation in neonates so as to predict hyperbilirubinemia as early as possible. So that Simple, safe and economic phototherapy as a treatment option is sufficient to save neonates life . Early detection of high bilirubin levels also helps neonate from developing dangerous consequences like kernicterus. This can be a reducing measure of infant mortality rate, an universally accepted indicator of health status.

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