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Study of Correlation of Cord Blood Bilirubin with Neonatal Hyperbilirubinemia

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Abstract

Introduction: Neonatal Hyperbilirubinemia (NH) is a universal problem affecting nearly 60% of term and 80% of preterm neonates during first week of life. Early discharge of healthy term newborns is a common practice because of medical, social and economic constraints. Insignificant number (6.5%) of babies, NH is a cause for readmission. The present study was conducted to correlate the Cord Blood Bilirubin (CBB) level with subsequent NH. **Methods:** Study was performed at the Department of Pediatrics in a Medical College Hospital and Research Centre. Intramurally delivered, 113 Healthy full-term newborns during 1-year period were prospectively enrolled. CBB was estimated. Serum Bilirubin estimation was done at 48 hours and 5 day of age and later if required. **Results:** Significant NH in our study is 3.5%. Mean total bilirubin on second postnatal day was 10.58 mg/dl and on fifth post natal day was 10.81 mg/dl. Using CBB level of ≥3 mg/dl as a cut-off, NH can be predicted with sensitivity of 100%, specificity of 98.17 %, positive predictive value of 66.67 % and negative predictive value of 100%. **Conclusion:** A 100% Negative Predictive Value in the present study suggests that in Healthy Term babies (without RH and ABO incompatibility with Cord Blood Bilirubin ≤3mg/dl) cord serum bilirubin can help to identify those newborns who are unlikely to require further evaluation and intervention. These newborns can be discharged with assurance to Parents. Babies with CBB level ≥3mg/dl should be followed more frequently.

Keywords: Cord Bilirubin, Hyperbilirubinemia, Newborns, Neonate

1. Introduction

Jaundice in newborn is a very common problem. Neonatal Hyperbilirubinemia (NH) may lead to kernicterus in otherwise healthy newborns. This can be easily prevented if excessive hyperbilirubinemia for age is promptly identified and appropriately treated[2,3]. Newborns can be screened for severity of bilirubinemia before hospital discharge which may help in early detection of the newborns at risk for excessive hyperbilirubinemia during the first week of life[4].

It is difficult to predict which of these newborns are at risk for developing significant hyperbilirubinemia (Total Serum Bilirubin ≥ 15mg/dl)[5] Significant hyperbilirubinemia is usually found in 3% of normal term babies[6]. Depending on various methods of bilirubin estimation in different laboratories, the frequency of breast feeding,ethnic makeup of people and regional variations the incidence of hyperbilirubinemia changes[7-9]. The severe jaundice and kernicterus has been found in some healthy full term newborns dischared early with no apparent hemolysis.[10]

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The American Academy of Pediatrics (AAP) recommends that newborns discharged within 48 hours should have a follow-up visit after 2-3 days to detect significant jaundice and other problems[11]. In developing countries like India, this recommendation is not practical due to limited follow up facilities.

Early treatment of jaundice with phototherapy is effective, simple and cheap as compared to the treatment of severe neonatal jaundice with exchange transfusion which is time consuming, costly, associated with complications and requires skilled personnel.

Thus the early prediction of jaundice offers an attractive option for picking up babies at risk of NH. Many investigators have tried to find a simple marker to predict hyperbilirubinemia and its subsequent course in newborns like cord bilirubin estimation[12,13], bilirubin estimation during 6 to 24 hours of age[14-17], predischarge hour specific bilirubin estimation[18] and transcutaneous bilirubin measurement[19-22].

Cord Bilirubin levels are easy to perform and may offer an attractive predictive marker for hyberbilirubinemia occurring later on.

It is with this view that the present study is undertaken to evaluate the predictive ability of cord bilirubin levels for subsequent hyperbilirubinemia in healthy term newborns.

2. Material and Methods

This is an Observational Study conducted in Department of Pediatrics of Medical College and Tertiary Health Care Centre from August 2012 to December 2014. Minimum 113 healthy full-term newborns were included after satisfying eligibility criteria. All full term neonates (Gestation age ≥37weeks to 42 weeks) irrespective of mode of delivery are included in our study and newborns having risk factors for development of severe hyperbilirubinemia like jaundice observed in first 24 hrs, ABO and/or Rh incompatibility, cephalohematoma or significant bruising, significant co morbidities requiring N.I.C.U. admission are excluded from our study.

Written informed consent is obtained from parents or guardian.

Detailed obstetric and medical history of mother is obtained and each newborn is assessed for confirmation of gestational age by New Ballard Score. Cord blood sample is collected and is used for following investigations:

1. Haemoglobin and Hematocrit.
2. Blood group and Rh factor
3. Serum bilirubin-Total
   Direct
   Indirect

For the present study "Cord Blood Hyperbilirubinemia" is defined as cord blood total bilirubin level ≥3mg/dl.[1]

Venous blood samples of the neonates are collected at 48 hours and at five days after birth. Following investigations are carried out on these samples:

1. Haemoglobin and Hematocrit.
2. Serum bilirubin- Total
   Direct
   Indirect

The serum bilirubin levels are monitored more frequently if required.

Blood sample collected was stored away from light. The sample was refrigerated between 2-8 degree C till serum bilirubin estimation is done. Serum bilirubin estimation was done within 12 hours of collection of sample by Diazotized sulfanilic test.

This method for bilirubin estimation is based on principle that Bilirubin reacts with diazotized sulphanilic acid in acidic medium to form pink coloured azobilirubin with absorbance directly proportional to bilirubin concentration. Direct Bilirubin, being water soluble directly reacts in acidic medium. However indirect or unconjugated Bilirubin is solubilised using a surfactant and then it reacts similar to direct Bilirubin.

Additional investigations are done as per the case. The findings of investigations are analysed by using statistical software.

3. Results

The following results were made from the study. An Observational study consisted of 113 healthy term newborns that were followed up for first 5 postnatal days. The study results were analysed using appropriate statistical methods.

Table 1. Study population and significant jaundice

	Significant Jaundice	
Total	Number	Percentage
113	4	3.5%

Table 2. Maternal Details (N = 113)

Mothers details	Number of Mothers	Total%	Significant Jaundice%
Mother age in years			
18-20	19	16.8	5.3
21-30	90	79.6	3.3
31-40	4	3.5	Nil
Parity			
Primi	57	50.44	1.8
Multi	56	49.55	5.4
Blood group			
A+	32	28.3	6.3
B+	36	31.8	Nil
O+	33	29.2	6.0
AB+	12	10.6	Nil
Total	113	100.0	

Table 3. Details of Neonates Studied (N 113)

Details of Neonates	Number of Neonates	Total %	Significant Jaundice %
Gender			
Male	57	50.44	3.5
Female	56	49.55	3.6
Weeks of Gestation			
37-38	87	77.0	4.6
39-40	26	23.0	Nil
Birth weight(kg)			
2.50-3.00	90	79.6	4.4
3.01-3.50	20	17.7	Nil
3.51-4.00	3	2.7	Nil
Blood group			
A+	28	24.8	7.1
B+	37	32.7	5.4
O+	33	29.2	Nil
AB+	15	13.3	Nil
Total	113	100.0	

Table 4. Effect of Oxytocin Induction on Jaundice

Oxytocin Induced	Number of neonates	Total %	Significant Jaundice %
Yes	50	44.2	6.0
No	63	55.8	1.6
Total	113	100.0	

Table 5. History of neonatal jaundice in previous siblings

H/O Neonatal Jaundice	Number of neonates	Total %
Yes	2	3.6
No	54	96.4
Total	56	100.0

Table 6. Bilirubin, Haemoglobin and Pcv Profile of the Study Population

	Minimum	Maximum	Mean	SD
Cord Blood Total Bilirubin	0.60	3.90	2.09	0.50
Day 2 Total Bilirubin	3.40	20.20	10.58	2.54
Day 5 Total Bilirubin	5.50	21.00	10.81	2.81
Haemoglobin	12.00	20.90	15.67	1.74
PCV	38.00	58.00	46.08	4.43
Day 2 Haemoglobin	12.50	18.00	14.51	1.22
Day 2 PCV	34.00	55.00	43.29	3.36
Day 5 Haemoglobin	12.54	18.00	14.82	1.16
Day 5 PCV	39.00	51.00	44.45	2.68

Table 7. Comparative evaluations of cord, day 2 and day 5 total bilirubin, haemoglobin and PCV

	Cord	Day 2	Day 5
Total Bilirubin	2.09±0.50	10.58±2.54	10.81±2.81
Haemoglobin	15.67±1.74	14.51±1.22	14.82±1.16
PCV	46.08±4.43	43.29±3.36	44.45±2.68

Table 8. Diagnostic predictability of cord blood total bilirubin of >3 mg/dl for hyperbilirubinemia at 48 hours

	Serum bilirubin (mg/dl) at 48 hrs of life	
Cord bilirubin at birth(mg/dl)	≥15	<15
≥3	4	2
<3	0	107

Diagnostic statistics	
TruePositive	4
FalsePositive	2
Falsenegative	0
Truenegative	107
Sensitivity(%)	100
Specificity(%)	98.17
PPV(%)	66.67
NPV(%)	100

The incidence of significant hyperbilirubinemia in our study population is 3.5 %. Significant jaundice is defined as TSB ≥ 15 mg/ dl at 48 hours of life (Table 1).

4. Discussion

In most of the neonates hyperbilirubinemia is a common problem. During the 1st week of life jaundice is seen in approximately 60% of term infants and 80% of preterm infants. Under normal circumstances, the umbilical cord serum (Table 2, 3) indirect bilirubin is 1-3 mg/dl and rises at a rate of <5 mg/dl/day; thus jaundice becomes visible on the 2nd or 3rd day, usually peaking between the 2nd and 4th days at 5-6 mg/dl and decreasing to <2 mg/dl between the 5th and 7th days of life[3] (Table 5-7).

Our study presumption was that a high serum bilirubin level at birth would also predict a high peak later in life. Our aim was to quantify the relationship between Cord blood bilirubin with peak serum bilirubin levels of the first five days. We chose cord blood estimation for initial serum bilirubin estimation as it is easy and a non invasive way and the results are available within few hours after birth.

The role of oxytocin in hyperbilirubinemia-Oxytocin has anti-diuretic and saluretic effects and thus causes hypo-osmolality and hyponatremia in the mother. These biochemical changes are aggravated when oxytocin is given with dextrose solution which was electrolyte free. This hypo-osmolality gets transferred transplacentally to foetus and causes increased red blood cells osmotic fragility. These swollen red blood cells gets easily destroyed in spleen and results in increased bilirubin production (Table 4).

The increased cases of bilirubin related neurological damage occurred as a result of early hospital discharge of newborns. Therefore, it is must to have an easy and safe test to identify babies who are at risk for significant jaundice and will help in avoiding the fatal outcome.

To address this issue AAP recommends that all newborns that were discharged within 48 hours of birth should be followed up within 2 to 3 days of discharge to hospital, health worker or at home. It will be very difficult to document the benefits of this policy, given the rare incidence of kernicterus and less chances of adapting the advice especially in lower socioeconomic and rural areas.

Experience suggests that asking mothers to look for yellowish discoloration (jaundice) in newborns is not reliable. Despite such instructions, it is difficult to recognize significant jaundice for many parents.

Unfortunately, the presence of severe jaundice for age is often missed clinically, which means that the trigger for measuring the first serum bilirubin level and deciding subsequent recommendation is not set. This is a potentially a serious problem. Jaundice appears at various intervals in newborns after birth and ability to notice its severity, approximate range with cephalocaudal progression has been a topic of study since 60 years. Additionally in most of the recently reported healthy term newborns that developed kernicterus, significant jaundice was almost certainly present before the first hospital discharge, judging from the height of TSB for age in hours at readmission. Either the early icterus had not been noted or its pathologic intensity for postnatal age was not appreciated.

Currently we do not have a reliable method of anticipating such levels of hyperbilirubinemia. Unfavourable outcomes can be prevented by regular, close and frequent follow up after birth and discharge from hospital, but to prevent rare cases of kernicterus to approach to surveillance of the newborn that is substantially more rigorous than has been practiced. The benefits, costs, feasibility and risks of such an approach need to be determined.

Collection of umbilical cord blood is simple, easy and not associated with any pain. Most important is that the results of tests are available within hours of birth. Thus the babies who are discharged within few days postnatally can be assessed for risk of hyperbilirubinemia in a non-invasive way at birth. Using Cord blood Bilirubin values may help to predict babies with low risk for hyperbilirubinemia and minimize an unnecessary stay in hospital.

Keeping these factors in mind our study was conducted on healthy full term neonates with non-hemolytic jaundice. We have considered peak serum bilirubin level >15 mg/dl as "hyperbilirubinemia" since specific treatment is usually considered at or above this level. However, some neonatologists initiate phototherapy at slightly lower serum bilirubin levels, especially if they suspect a

rising trend. Therefore, we have also predicted treatment with phototherapy.

5. Incidence of Hyperbilirubinemia

Incidence of hyperbilirubinemia varies from 3.5% to 12.8% in various Studies. Incidence of hyperbilirubinemia in the present study is 3.5% which is le-ast among all the studies because our study group consisted of neonates with no risk factors.

Other studies also reported the relation between raising levels of cord bilirubin and increased incidence of significant hyper bilirubinemia in later life. In ABO or non-ABO situation raised cord blood bilirubin indicates ongoing hemolysis while in mothers womb. These babies are more likely to develop hyperbilirubinemia (Table 9-11).

In the present study using serum bilirubin levels ≥ 3 mg/dL in the cord blood, hyperbilirubinemia could be predicted with sensitivity of 100%, specificity of 98.17 %, and positive predictive value of 66.67 % and Negative predictive value of 100% (Table 8).

6. Conclusion

In postnatal wards hyperbilirubinemia is one of the common problems seen. Neonatal hyperbilirubinemia occurs

Table 9. Comparison of incidence of hyperbilirubinemia

Studies	Year	No.Of Cases	Incidence of Hyperbilirubinemia
Palmer et al.[23]	1983	41057	10.70
Phuapradit et al. [24]	1993	7644	8.35
Awasthi et al.[14]	1998	274	12.80
Alpay et al. [15]	2000	498	12.05
Agarwal et al. [16]	2002	213	10.30
Knupfer M et al. [13]	2005	1100	10.60
Amar T et al. [25]	2005	200	9.5
Randev S et al. [17]	2010	200	12
Present Study	2012	113	3.5

Table 10. Comparison of cord serum bilirubin and significant jaundice

Studies	Year	No. of Cases	Umbilical cordbilirubin	Incidence of Hyperbilirubinemia
RosenfeldJ et al.[26]	1986	-	<2mg >2mg	4% 25%
Knudsen et al.[27]	1989	291	<1.17mg >2.34mg	2.9% 85%
Rataj et al.[28]	1994	800	≤1mg% >2.5mg%	2.4% 89%
Suchonska B et al.[29]	2004	-	<1mg%	0%
Bernaldoet al.[12]	2004	380	≥2mg	53%
Amar T et al.[25]	2005	200	>2 mg/dl	9.5%
Knupfer et al.[13]	2005	1100	<1.17 1.17–1.75 1.75–2.34 >2.34	0% 0.30% 3.4% 8.6%
Present study	2012	113	<3mg >3mg	0% 3.3%

Table 11. Studies on the predictive ability of cordblood bilirubin level and the neonatal hyperbilirubinemia

Studies	CutoffCord STB (mg/dL)	Cutoff Neonatal Hyperbilirib-inemia (mg/dL)	Sensitivity	Specificity	Positive PredictiveValue	Negative PredictiveValue
Amar Taksande et[25]al(2005)	>2	≥17	89.5%	85%	38.8%	98.7%
Knudsen[27](1989)	>2.35	>15	13%	99%	85%	72%
ZakiaNaharet al.[30](2009)	≥2.5	≥17	77%	98.6%		96%
Sun et al.[31](2007)	>2	≥17	68%		45.08%	
RudySatrya et al.[32](2009)	≥2.54	≥12.9	90.5%	85%		
Present (2012)	≥3	≥15	100%	98.17%	66.67%	100%

in 5-10 % of healthy term infants. Upto 4% of term newborns who are readmitted to the hospital during their first week of life, approximately 85% are readmitted for jaundice.

Oxytocin has ability to develop neonatal hyperbilirubinemia by inducing hemolysis so it should be used with caution.

Early identification of at risk newborn for significant hyperbilirubinemia byusing simple predictors can help to prevent possible bilirubin induced neurological damage.

A 100% Negative Predictive Value in the present study suggests that in healthy term babies (without RH and ABO incompatibility with Cord Blood Bilirubin<3mg/dl) cord serum bilirubin can help to identify those newborns who are unlikely to require further evaluation and intervention.

Babies with Cord Blood Bilirubin level ≥3mg/dl should be followed more frequently to reduce morbidity and mortality due to neonatal hyperbilirubinemia.

Our study sample did not have a heterogeneous group of neonates. This is the strength of our study. It means that the Prediction test (48 hrs TSB ≥15 mg/dl) developed by us can be applied to the neonates of local rural population on whom it was developed.

Thus prediction of neonatal hyperbilirubinemia will have widespread implication especially in our rural setup.

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