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Research Article

Prediction of significant hyperbilirubinemia using 24 hour serum bilirubin

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ABSTRACT

Background: Neonatal hyperbilirubinemia (NH) is a common 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 various constraints in resource poor settings. The present study was conducted to determine predictive ability of 24 hour serum bilirubin for subsequent significant hyperbilirubinemia and to identify risk factors in healthy term newborns.
Methods: The present study was conducted on 250 term healthy neonates delivered at tertiary care hospital. Serum bilirubin level was estimated at 24±2 hours of age. The main outcome measured was 'significant' hyperbilirubinemia requiring treatment (phototherapy/exchange transfusion).The newborns were followed up clinically till 5th day of life. Serum bilirubin was estimated clinically as indicated and on day 5 of life.
Results: By ROC analysis 24 hour serum bilirubin level of >4.75 mg/dl was found to have highest sensitivity of 82.5%, specificity of 81.9%, positive predict value of 46.5% and negative predict value of 96.1%. Newborn babies with 24 hours serum bilirubin level of >4.75 mg/dl had a significant risk of developing neonatal hyperbilirubinemia, as observed by the serum bilirubin levels on day five. Mode of delivery, order of birth and oxytocin induction during labour associated with significant risk of hyperbilirubinemia.
Conclusions: 24 hour bilirubin level of more >4.75mg/dl can reliably predict neonatal hyperbilirubinemia in healthy term neonates.

Keywords: 24 hour bilirubin, Neonatal hyperbilirubinemia, Risk factors

INTRODUCTION

Neonatal jaundice is a cause of concern to parents and most common reason for seeking consultation after discharge.[1] Sixty percent of the term healthy neonates have clinical jaundice in first week of life 6.1% healthy term newborns without identified risk factors have a maximal serum bilirubin level >12.9 mg/dl.[2] In majority of cases it is benign and does not require treatment. Severe hyperbilirubinemia is associated with neurodevelopmental handicaps and kernicterus. Kernicterus is reported in otherwise healthy newborns.[3] Bilirubin toxicity to immature brain in term newborns can be easily prevented if identified early. Early initiation of treatment is cost effective and highly effective in preventing the neurological sequelae. Early discharge of healthy term newborns is a common practice because of various constraints in resource poor settings.[4] Follow up of neonates discharged early is essential to identify neonates at risk of hyperbilirubinemia. The American Academy of Pediatrics (AAP) recommends that

newborns discharged within 48 hours should have a follow-up visit to detect significant jaundice and other problems.[5] Follow up cannot be assured universally in resource poor settings. Hence it of paramount importance to reliably predict and identify risk factors for neonates for development of severe hyperbilirubinemia. Various methods were used to identify significant hyperbilirubinemia. Cord blood bilirubin levels, predischarge hour specific bilirubin values and transcutaneous bilirubin estimation used by many investigators to accurately identify at risk neonates.[6-8] The ability of cord blood bilirubin level to predict severe hyperbilirubinemia in neonate is widely debated.[9,10] There have been reports of a significant correlation between 24 hour bilirubin values and subsequent development of severe Hyperbilirubinemia. There is paucity of studies regarding this in India.[11] Hence the present study was conducted to evaluate 24 hour serum bilirubin level for predicting significant hyperbilirubinemia.

The primary objective was to determine the predictive ability of 24 hours serum bilirubin for subsequent significant hyperbilirubinemia in healthy term newborns. Secondary objective was to identify at risk factors for significant hyperbilirubinemia.

METHODS

This cross sectional observational study was conducted at this hospital based prospective cohort study was conducted on 250 full term healthy newborns delivered at Maharajahs Institute of Medical Sciences (MIMS) Hospital , Vizianagaram India for a period of 2 years. Permission from hospital ethical committee was obtained.

Neonates with gestational age of >37week as measured by New Ballard's score and birth weight >2.5 kg were enrolled in study. Neonates with sepsis, birth asphyxia, IUGR, gross congenital anomalies and Rh incompatibility were excluded from this study.

All consecutive inborn neonates who fulfilled the inclusion criteria were recruited after taking consent form parents/mother. Clinical data was recorded in a specially designed proforma. Maternal data recorded include use of medications, blood group, and oxytocin induction during labour, maternal diabetes and pregnancy induced hypertension. Neonatal data recorded include mode of delivery, Apgar score at1mim and 5min, gender, weight, gestational age by modified Ballard score and occurrence of sepsis, respiratory distress and apnoea. Serum bilirubin and blood grouping of all neonates were estimated on venous blood sample collected at 24±2 hours of life. The newborns were followed up for 5 day period with daily physical examination according Kramer dermal zones. In case of clinical jaundice presenting before 5 days, serum bilirubin level was rechecked on the same day. Bilirubin estimation was done on fifth day in all neonates.

Serum bilirubin estimation was done by Diazo method. The neonates were followed up clinically every 12 hours for 5 days, in case of early discharge they were followed every 24 hours for 5 days. Next bilirubin estimation was done whenever clinical suspicion of jaundice was present. Primary outcome was significant hyperbilirubinemia defined as requiring phototherapy or exchange transfusion according to AAP criteria.

Analysis of data

Descriptive statistics were used to describe baseline variables. Categorical outcome variables were analyzed by Chi square test with continuity correction or Fisher's exact test, wherever one or more expected cell size was less than 5. Receiver Operating Characteristics (ROC) curve analysis was carried out to determine the cut off for 24 hour serum bilirubin level for identifying neonates at risk. All the neonates were classified into four groups according to first day serum bilirubin <3mg/dl (group-1), 3-4.9mg/dl (group-2), 5.0-6.9mg/dl (group-3), and >7mg/dl (group-4) to assess the significance. 'p' values with significance of <5% were considered statistically significant. The analysis was carried out using the statistical package for the social sciences (SPSS 15) program for windows.

RESULTS

Two hundred fifty healthy full-term neonates were enrolled in the study. Baseline characteristics of the included subjects are shown in Table 1. There were 140 (56%) male neonates. Forty newborns developed significant hyperbilirubinemia. 135 (54%) were delivered by normal vaginal delivery (NVD) and 115 (46%) delivered by LSCS.

Table 1: Baseline characteristics of the study population.

Characteristics	Number	Percentage
Type of delivery		
Vaginal delivery	135	54%
LSCS	115	46%
Gender		
Male	140	56%
Female	110	44%
Oxytocin use		
used	80	32%
Not used	130	68%
Parity		
1	112	44.8%
2	76	30.4%
3	42	16.8%
ABO incompatibility		
Present	42	16.8%
Not present	208	83.2%

All the neonates were classified into four groups depending on the 24 hour serum bilirubin levels <3mg/dl (group-1), 3-4.9mg/dl (group-2), 5-6.9mg/dl (group-3), and >7mg/dl (group-4). Majority 130 of newborns had mean 24hr bilirubin level between 3-4.9mg/dl. 63 (21.2%) newborns had 24 hours blood bilirubin level between <3mg/dl. 43 newborns had 24 hours blood bilirubin level between 5-6.9 mg/d. 14 neonates had 24 hours bilirubin levels >7mg/dl. The range of bilirubin value within 24 hours was 2.1 to 8.1mg/dl. Among 40 newborns who develop significant hyperbilirubinemia, majority were in group-3 (52.5%) and only two in group-1 (5%). There was statistically highly significant (p<0.001) association between requirement of phototherapy and higher 24hours serum bilirubin levels. Number of newborns requiring phototherapy proportionately increased as the 24hrs serum bilirubin level increases i.e. from 3.2% in group-1 to 71.4% group-4.

Receiver operating characteristics curve analysis was done for 24 hour serum bilirubin to identify best cut off for prediction of significant hyperbilirubinemia. 24 hour serum bilirubin level of >4.75 mg/dl was determined to have the highest predicting ability according to ROC curve (p<0.001) to predict the newborns who develop significant hyperbilirubinemia. In this study, using 24 hour serum bilirubin level of >4.75 mg/dl hyperbilirubinemia could be predicted with sensitivity of 82.5%, specificity of 81.9%, positive predict value (PPV) of 46.5% and negative predict value (NPV) of 96.1%. Association between 24 hour ROC curve analyzed serum bilirubin cut of value >4.75mg/dl and significant neonatal hyperbilirubinemia shown in Table 2, Figure 1. The area under the ROC curve is 0.88, which makes the test fall under the category of a good test. 24 hour serum bilirubin level of >4.75 mg/dl cut off value is chosen on the ROC analysis to predict significant neonatal hyperbilirubinemia. The values characterizing the predictive ability of 24 hour bilirubin as predictor for the future development of significant hyperbilirubinemia are show in (Table 3).

Table 2: Association between first day serum bilirubin and significant neonatal hyperbilirubinemia.

First day serum bilirubin levels	Total	Hyperbilirubinemia		'p' value
		Yes	No	
Group 1 (<3mg/dl)	63	2 (3.1%)	61	<0.001
Group 2 (3-4.9mg/dl)	130	7 (5.3%)	123	
Group 3 (5-6.9mg/dl)	43	21 (48.8%)	23	
Group 4 (>7 mg/dl)	14	10 (71.4%)	4	

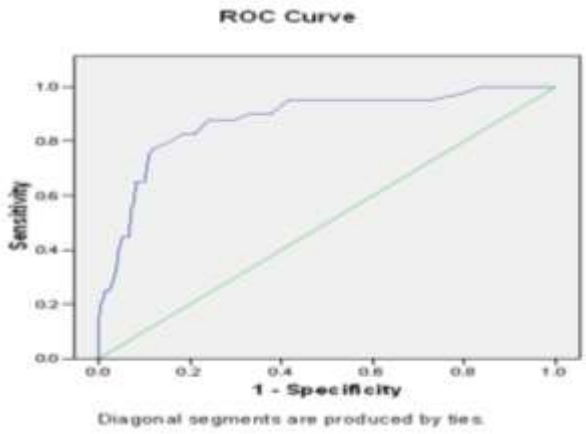

Figure 1: Receiver operating characteristics curve analysis for first day serum bilirubin level.

Table 3: Predictive ability of 24 hours serum bilirubin for assessment of severe hyperbilirubinemia.

First day serum bilirubin levels Mean	Total	Hyperbilirubinemia		'p' value
		Yes	No	
<4.75mg/dl	**179**	7 (3.9%)	172	<0.0001
>4.75mg/dl	**71**	33 (46.4%)	38	

The data was analysed for risk factors. There is no significant difference ('p' value 0.63, chi-square value 0.23) between the neonatal gender and significant hyperbilirubinemia (Table 4). Among 40 newborns with significant hyperbilirubinemia 25 (22%) cases were delivered by LSCS and 15 (11%) cases were delivered by NVD. There is statistically significant association ('p' value 0.022) between the neonatal significant hyperbilirubinemia and the mode of delivery. In this study 112 (44.8%) newborn were first order birth, 76 (30.4%) were second order and 62 (22.8%) were third order. In the present study 26 (23.2%) neonates of first order, 9 (11.8%) of second order and 5 (8%) of third order birth developed significant hyperbilirubinemia. There is statistically significant association (p=0.016) between the neonatal significant hyperbilirubinemia and the order of delivery. Labour was augmented in l 80 (32%) using oxytocin. 19 (23.7%) cases developed significant hyperbilirubinemia. In the present study there is statistically significant association (p value = 0.022) between the neonatal significant hyperbilirubinemia and oxytocin induction. There was setting for ABO incompatibility in 42 (16.8%). Among them 12 (28.6%) neonates had developed neonatal significant hyperbilirubinemia. There is statistically significant association ('p' value 0.015, chi-square value 5.94) between the neonatal significant hyperbilirubinemia and the ABO incompatibility.

Table 4: Distribution of cases of hyperbilirubinemia according to different variables.

	Total	Hyperbilirubinemia		'p' value
		Yes	No	
Gender				
Male	140	21 (15%)	119	0.63
Female	110	19 (17%)	91	
Route of delivery				
LSCS	115	25 (22%)	90	0.022
NVD	135	15 (11%)	120	
Birth order				
1	112	26 (23.2%)	86	0.016
2	76	9 (11.8%)	67	
3	62	5 (8%)	57	
ABO incompatibility				
Present	42	12 (28.6%)	30	0.015

DISCUSSION

Early discharge has become a common practice due to more deliveries and limited neonatal care facilities. There are reports of bilirubin induced brain damage occurring in healthy term neonates.[12,13] Hyperbilirubinemia is the common cause of readmission of neonates discharged early. About 8-11% of well-baby population may require intervention for hyperbilirubinemia and nearly 30% require continued mointering.[6] Accurate and reliable prediction of at risk neonates will allow early discharge of low risk neonates and follow up of high risk neonates. Simple, non-invasive and in expensive methods can be implemented in high risk neonates before the bilirubin reaches the danger level. Various strategies have been adopted to predict babies likely to develop neonatal hyperbilirubemia.[2] Utility of 24 hours bilirubin level in accurately predicting newborns at risk is widely reported.[14] This study is aimed to determine the risk factors and 24 hour serum bilirubin level to accurately predict significant hyperbilirubinemia in healthy term neonates. Our study hypothesis was that 24 hour serum bilirubin level can predict significant hyperbilirubinemia in healthy term neonates. Peak serum bilirubin level >15 mg/dl as "significant Hyperbilirubinemia" since specific treatment is usually considered at or above this level.[5] Out of 108 neonates admitted 56% are males compared to 44% females. No statistically significant association between significant hyperbilirubinemia and sex of neonates is found. Taksande A et al, in a study on 200 neonates with 82 males and 118 females found no association between gender of the newborn and the neonatal hyperbilirubinemia (≥15mg/dl).[15] In contrast study by Satrya R et al, showed significant association between the sex of the newborn and neonatal hyperbilirubinemia. They observed significant hyperbilirubinemia in male neonates.[16]

In this study, majority (44.8%) of newborn were first order birth. Significant hyperbilirubinemia developed in neonates delivered to primiparous women. This is similar to the findings of a study by Phelan et al, where primiparous mothers are more likely to have jaundiced infants.[17]

Out of 250 newborns admitted only 115 babies delivered by caesarean section. High percentage of newborns has delivered normally are enrolled in this study. Significant hyperbilirubinemia is observed in caesarean delivered neonates. Review of literature showed conflicting results on significant hyperbilirubinemia and mode of delivery. Most of studies are done on cord blood samples. In study by Singhal V et al, observed statistically significant hyperbilirubinemia in caesarean delivered babies.[18] In contrast studies by Taksande A et al, Rostami et al, Knudsen A, found no association between mode of delivery and significant hyperbilirubinemia.[15,19-20] This does not match with the inference of this study.

138 (55.2%) mothers are below the age of 25 Years and 14 (5.6%) are above the age of 30 years. No statistically significant association is found between significant hyperbilirubinemia and maternal age. This is in agreement with a study done by Singhal V , et al and Srivastav, et al[2].[18,21]

In the present study total 250 cases, 80 (32%) cases are managed with oxytocin during labor. Oxytocin induces hyponatremia and hypo-osmolality in the mother by virtue of its anti-diuretic and saluretic effects. Transplacentally transmitted hypo-osmolality in the fetal blood, leads to enhanced osmotic fragility of the red blood cells. The swollen and hyper fragile erythrocytes are easily trapped by the spleen resulting in net higher bilirubin production. Statistically significant association observed between oxytocin induction of labour and significant hyperbilirubinemia. The present study correlated with the studies of Oral E, et al and Awasthi et al.[22,23]

In the present study, 24 hour serum bilirubin value of 4.75 mg/dL was considered as cut-off to predict subsequent hyperbilirubinemia requiring phototherapy in view of an increase in the percentage of neonates developing hyperbilirubinemia above this value (3.9% - 46.4%) between the two groups. This value is higher than that in the study by Trisiah R et al, and lower than that used in the study by Alpay et al.[24,25]

Present study shows 24 hour serum bilirubin is an useful indicator of subsequent neonatal hyperbilirubinemia and aids in identifying the low risk group children with 24 hour bilirubin <4.75 mg/dl. NPV in this low risk group can prove useful in using this parameter for making decisions regarding early discharge or request for review of the newborns for evaluating neonatal hyperbilirubinemia.

For optimal utilization of the limited neonatal care facility available in our country, it is essential to have practical guidelines to predict which healthy newborn

would develop significant hyperbilirubinemia and to avoid preventable neurological damage. From the present study, it can be concluded that 24 hour bilirubin >4.75mg/dl will help predict nearly all healthy term newborns that have significant hyperbilirubinemia and will require a phototherapy treatment later during first few days of life. Oxytocin, induction of labour, male gender and order of delivery must consider in healthy neonates before discharge. The main limitation of this study was small sample size. Further clinical follow up of neonates have done which is not ideal. Ideally follow up measuring serum levels of bilirubin would have been more appropriate.

CONCLUSION

The present study proves that a 24 hour total serum bilirubin (TSB) of less than 4.75 mg/dl predicts the risk of subsequent Hyperbilirubinemia. Oxytocin use, male sex and order of delivery are risk factors while contemplating early discharge of healthy neonates. To ease the burden on limited neonatal health care facilities it is necessary to have practical guidelines to predict significant hyperbilirubinemia in neonates.

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REFERENCES

1. Anthony JP, Barbara JS. The new born infant, Digestive system disorders: Jaundice and hyperbilirubinemia in the newborn. In: Richard E. Behrman, Robert M. Kliegman, Hal B., Bonita F. Stanton, Editors, Nelson Textbook of Pediatrics: 18th ed. Philadelphia: Saunders Elsevier; 2008:756-66.
2. Mary LP, Gregory, Martin CR, Cloherty JP. Neonatal Hyperbilirubinemia. In Cloherty JP, Eichenwald EC, Hansen AR, Stark AR eds. Manual of neonatal care: 7th Ed. New Delhi: Wolters Kluwer.2012:304-39.
3. Maisles MJ, Newman TB. Kernicterus in otherwise healthy breast-fed Term Newborns. Pediatrics. 1995;96:730-3.
4. Catz C, Hanson JW, Simpson L, Yaffe SJ. Summary of workshop: Early Discharge and Neonatal Hyperbilirubinemia. Pediatrics. 1995;96:743
5. American Academy of Pediatrics clinical practice guideline and subcommittee on hyperbilirubinemia. Management of hyperbilirubinemia in the newborn Infant 35 or more weeks of Gestation. Pediatrics.2004;114:297-316.
6. Bhutani VK, Jhonson L, Sivieri EM. Predictive ability of a predischarge Hour- specific serum bilirubin for subsequent significant Hyperbilirubinemia in healthy term and near Newborns. Pediatrics. 1999;103:6-14.
7. Gupta PC, Kumari S, Mullick DN. Icterometer; useful screening tool for neonatal Jaundice. Indian Pediatr. 1991;28:473-6.
8. Kumar A, Faridi MM, Singh N, Ahmad SH. Transcutaneous bilirubinometry in the management of bilirubinemia in term neonates. Indian J Med Res. 1994;99:227-30.
9. Rosenfeld J. Umbilical cord bilirubin levels as a predictor of subsequent hyperbilirubinaemia. J FAM Pract. 1986;23(6):555-8.
10. Risemberg HM, Mazzi E, MacDonald MG, Peralta M, Heldrich F. Correlation of cord bilirubin levels with hyperbilirubinaemia in ABO incompatibility. Arch Dis Child. 1977;52:219-22.
11. Randev S, Grower N. Predicting neonatal hyperbilirubinemia using first day serum bilirubin levels. Indian J Pediatr. 2010;77:147-50.
12. Penn AA, Enzmann DR, Hahn JS, Stevenson DK. Kernicterus in a full term infant. Pediatrics. 1994;93:1003-6.
13. Newman TB, Maisles MJ. Does hyperbilirubinemia damage the brain of healthy full-term infants? Clin Perinatol. 1990;17:331-58.
14. Seidman DS, Ergaz Z, Paz I, Laor A, Revel-Vilk S, Stevenson DK, et al. Predicting the risk of jaundice in full-term healthy newborns: a prospective population based study. J Perinatol. 1999;19:564-7.
15. Amar T, Krishna V, Manish J, Preeti Z, Suchita A, Sherin V. Prediction of the development of neonatal hyperbilirubinemia by increased umbilical cord blood bilirubin. Ind Medica. 2005;9(1):5-9.
16. Rudy S, Sjarif HE, Dida AG. Correlation between cord blood bilirubin level and incidence of hyperbilirubinemia in term newborns. Paediatrica Indonesiana. 2009;49(6):349-54.
17. Phelan JG, Taylor JA, Liu LL, Davis RL. Early newborn hospital discharge and readmission for mild and severe jaundice. Arch Pediatr Adolesc Med. 1999;153:1283-8.
18. Singhal V, Kamath N, Baliga BS, Unnikrishnan B. Cord blood bilirubin level, an early predictor of neonatal hyperbilirubinemia. Perinatology. 2012;13(1):1-8.
19. Rostami N, Mehrabi Y. Identifying the newborns at risk for developing significant hyperbilirubinemia by measuring cord bilirubin levels. J Arab Neonatal Forum. 2005;2:81-5.
20. Knudsen A. Prediction of the development of neonatal jaundice by increased umbilical cord blood bilirubin. Acta pediatr Scand. 1989;78(2):217-21.
21. Srivastava N, Pande US, Malik GK, Singh SS, Singh SK. A study of serum bilirubin in neonates in relation to the maternal age. Indian J Med Sci. 1999;53:158-61.
22. Oral E, Gezer A, Cagdas A, Pakkal N. Oxytocin infusion in labor: the effect different indications and the use of different diluents on neonatal bilirubin levels. Archgynecol Obstet. 2003;267(3):117-20.
23. Awasthi S, Rehman H. Early prediction of neonatal hyperbilirubinemia. Indian J Pediatr. 1998;65:131-9.

24. Rina T, Ekawaty LH, Achmad S. The first 24-hour bilirubin level as a predictor of hyperbilirubinemia in healthy term newborns. Pediatrica Indonesaina. 2003;43:5-6.
25. Alpay F, Sarici SU, Tosuncuk HD, Serdar MA, Inanç N, Gokcay E. The Value of First Day Bilirubin Measurement in Predicting the Development of Significant Hyperbilirubinemia in Healthy Term Newborns. Pediatrics. 2000;106(2):1-5.

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