Prediction of the Risk of Neonatal Hyperbilirubinaemia by Umbilical Cord Blood: A Prospective study.

Shalabh Kumar Agarwal[1]

[1]Associate Professor, Department of Paediatrics, TMMC & RC, TMU, Moradabad.

ABSTRACT

Background: The incidence of jaundice in first week of life is very common affecting about 55% of term and 82% of pre-term neonates. There should be specific guidelines for the early prediction of neonatal hyperbilirubinaemia by different available techniques. This will not only decrease the social, financial and medical burden but will also help in minimising the extent of brain damage. The aim of the present study is to confirm that umbilical cord blood bilirubin level is an important predictor of neonatal hyperbilirubinaemia. Besides this, the safe cut off value of bilirubin is also studied for early diagnosis of jaundice. **Methods:** It is an observational, prospective study in which the umbilical cord blood was collected for the estimation of serum bilirubin level and then again after 72 hours of life for estimation of serum total bilirubin. Statistical test using chi-square test of significance was applied and the predictive values (Sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) were calculated using the conventional formulae. **Results:** Various maternal factors (age, parity and mode of delivery) and neonatal factors (sex, gestational age and birth weight) can influence the incidence of neonatal jaundice. It was an interesting finding that the neonates who had high umbilical cord bilirubin level, developed neonatal jaundice in the first week of life. The sensitivity and specificity of the test were highest in case of group 4 (96.5%) and (96.2%) respectively. The positive predictive value was highest in group 4 (42%) and negative predictive value was highest in group 3 (94%). **Conclusion:** The bilirubin estimation of umbilical cord blood can be an important indicator of neonatal jaundice and helps in planning the management of neonate.

Keywords: Hyperbilirubinaemia, Neonate, Phototherapy, Umbilical cord blood.

INTRODUCTION

The yellowish discoloration of the skin and other tissues in a newborn baby is defined as neonatal jaundice. The bilirubin level of > 2 mg/dl in adults give the appearance of yellowish discoloration, whereas in neonates at least bilirubin level of > 5 mg/dl is required for the symptoms to appear.[1,2]

The common signs and symptoms which develop are yellowish discoloration of sclera of eye, skin of face and as the disease progresses it extends to chest and extremities. In severe cases, the increased bilirubin level can cause permanent brain damage.[3]

Name & Address of Corresponding Author
Dr. Shalabh Kumar Agarwal
Associate Professor,
Department of Paediatrics,
TMMC & RC, TMU, Moradabad.

Clinically the diagnosis is made by blanching the skin to visualize the underlying tissue. Infant whose palms and soles are yellow, have serum bilirubin level over 15 mg/dl, which is a severe case. In infants, jaundice can be measured using invasive or non-invasive methods.[4]

In the developing countries like India neonatal hyper-bilirubinaemia has become an important common cause for readmission in neonatal period. It has become an important topic of research to prevent the medical, social and economic burden. Early discharge of a healthy mother and baby is the common practice in developed countries. The same trend is now followed in India. The late onset of symptoms of jaundice is common. Thus it becomes essential to develop new methods for early diagnosis of this disease, in order to decrease the rate of readmission.[5-11]

The incidence of jaundice in first week of life is very common affecting about 55% of term and 82% of pre-term neonates. Usually the neonate develops the symptoms late and is cured with method like exchange transfusion. This method is time consuming, costly and usually needs proper mechanical set up as well as skilled manpower, which is usually not available in rural areas. If the disease can be diagnosed in early stage then it can be cured with phototherapy which is relatively cheaper and easier method.[12,13]

Now different studies are being conducted to develop new methods so that early prediction of neonatal jaundice can be made.[14-17] Sometimes,

normally the serum bilirubin level of >15 mg/dl is found in 3-5% of newborn. Various other factors also influence the incidence of hyperbilirubinaemia like racial variation, standard laboratory parameters and breast feeding. Recently various studies have been conducted to develop new methods and parameters for making the diagnosis of neonatal hyperbilirubinaemia like serial bilirubin measurement in first 24 hours, trans-cutaneous bilirubin level, measurement of End-Tidal Carbon Monoxide (ETCO) and umbilical cord blood bilirubin level.[18]

Various researchers believe that there should be specific guidelines for the early prediction of neonatal hyperbilirubinaemia by different available techniques. This will not only decrease the social, financial and medical burden but will also help in minimising the extent of brain damage.[16-20]

The aim of the present study is to confirm that umbilical cord blood bilirubin level is an important predictor of neonatal hyperbilirubinaemia. Besides this, the safe cut off value of bilirubin is also studied for early diagnosis of jaundice.

MATERIALS AND METHODS

It is an observational, prospective study conducted in department of paediatrics, in which 200 healthy, full term babies were included. The study was approved by research ethical committee and written consent was taken by the parents. All the babies who were full term, having birth weight > 2.5 kg and apgar score at one minute of > 7/10 were included in the study. Babies who were preterm, weight of less than 2.5 kg, birth asphyxia, major congenital anomalies and who were sick besides jaundice were excluded from the study.

Proper ante natal history of mother was taken, complete clinical examination of newborn was done and basic investigations were done. During delivery of the baby, the umbilical cord blood was collected in a clean vial for the estimation of serum bilirubin level. Under aseptic precaution 1 mL of venous blood was drawn in a plain vial from all the babies enrolled in study on or after 72 hours of life for estimation of serum total bilirubin. Then the newborns were assessed clinically after 5 days of delivery for the signs and symptoms of jaundice.

Bilirubin estimation was done by Diazo method which is based on the principle that bilirubin reacts with diazotised sulphanilic acid in acidic medium to form pink coloured. Direct bilirubin, being water soluble directly reacts in acidic medium. However, indirect bilirubin is solubilised using a surfactant and then reacts similar to direct bilirubin. According to AAP guidelines significant jaundice is defined as the bilirubin level of >15 mg/dL, which requires emergency treatment.

On the basis of the umbilical cord bilirubin level, the neonates were divided into four groups:

Group 1: < 1mg/dl
Group 2: 1 - 2mg/dl
Group 3: 2.1 -3mg/dl
Group 4: >3 mg/dl

Statistical analysis: The data was compiled and tabulated in Microsoft excel sheet. Statistical test using chi-square test of significance was applied and the predictive values (Sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) were calculated using the conventional formulae. The p values with significance of 0.05 were considered statistically significant.

RESULTS

50 neonates out of 200 had normal bilirubin level even after 72 hours of birth and developed no signs and symptoms of jaundice clinically after 5 days of delivery, so these newborns were excluded from the study. 32 newborns developed significant jaundice (bilirubin level >15 mg/dL) and they were treated with phototherapy.

Table 1: Effect of maternal factors on the incidence of severe neonatal jaundice.

Maternal parameter		No. of subjects developing jaundice		No. of subjects undergoing phototherapy	
		Total (n)	Percent (%)	Total (n)	Percent (%)
Maternal age (years)	<25	96	64	21	65.6
	25-35	35	23.3	8	25
	>35	19	12.6	3	9.3
Parity	1	82	54.6	15	46.8
	2	41	27.3	9	28.1
	3	17	11.3	7	21.8
	>3	10	6.66	1	3.1
Delivery mode	Vaginal	55	36.6	12	37.5
	Caesarean	95	63.3	20	62.5

Various maternal factors like age, parity and mode of delivery which can influence the incidence of neonatal jaundice were studied. 64% of neonates developed hyperbilirubinaemia whose mother's age was < 25 years, whereas only 19 % of neonates suffered from the disease when maternal age was > 35 years. Thus we can conclude that incidence of jaundice decreases with the increase in maternal age [Table 1]. Another important finding was that neonates of primigravida are more susceptible to neonatal jaundice as compared to multigravida. But these results were not statistically significant (p>0.05).

It was found that mode of delivery (vaginal/caesarean) also effects the incidence of neonatal jaundice. 62.5% of subjects delivered through caesarean section underwent phototherapy whereas only 37.5% subjects delivered vaginally were treated with phototherapy [Table 1]. This difference was found to be statistically significant (p<0.05).
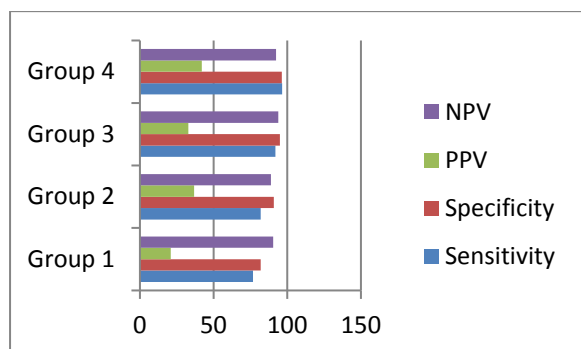
Table 2: Effect of neonatal factors on the incidence of severe neonatal jaundice.

Neonatal parameter		No. of subjects developing jaundice		No. of subjects undergoing phototherapy	
		Total (n)	Percent (%)	Total (n)	Percent (%)
Sex	Male	89	59.3	19	59.3
	Female	61	40.6	13	40.6
Gestational age (weeks)	36-40	59	39.3	12	37.5
	>40	91	60.6	20	62.5
Birth weight (kg)	2.0-2.5	77	51.3	15	46.8
	2.6-3.0	42	28	10	31.25
	>3.0	31	20.6	7	21.8

It has been found that certain neonatal factors like sex, gestational age and birth weight influence the incidence of neonatal hyperbilirubinaemia. 59.3% of males developed neonatal jaundice as compared to 40.6% of females, but this was not statistically significant (p>0.05). Neonates who were delivered at the gestational age of > 40 weeks were found to be more prone to develop neonatal hyperbilirubinaemia [Table 2]. It was also found that the chances of developing hyperbilirubinaemia is inversely proportional to birth weight of the neonate [Table 2].

Table 3: Prediction of developing neonatal jaundice on the basis of umbilical cord bilirubin level.

Groups of neonates on basis of cord bilirubin level (mg/dl)	Number of subjects (n)	Percent of subjects developing neonatal jaundice (%)	Percent of subjects undergoing physiotherapy (%)
Group 1	20	21	11
Group 2	45	38	29
Group 3	61	72	82
Group 4	24	70	89

Figure 1: Validity and Predictive Values of Cord bilirubin in Assessing Hyperbilirubinaemia.

The sensitivity of the test was highest in case of group 4 (96.5%) and lowest in group 1 (76.8%). The specificity was also highest in group 4 (96.2%) followed by group 3 (95%), 2 (90.8), and 1 (82%).

The positive predictive value of group 4 is 42% followed by 36.8%, 32.9% and 21% of group 2, 3 and 1 respectively. The negative predictive value was highest in group 3 (94%) and lowest in group 2 (89%) [Figure 1].

DISCUSSION

The literature suggest that normal serum bilirubin level at the time of birth is about 1-3 md/dl which rises at the rate of 5mg/dl/day. The peak levels are achieved about 2-4 days after birth and then finally decline in the bilirubin level is seen. Now the researchers believe that through these fluctuations in bilirubin level and by other methods like serial bilirubin measurement in first 24 hours, trans-cutaneous bilirubin level, measurement of End-Tidal Carbon Monoxide (ETCO) and umbilical cord blood bilirubin level, the prediction of neonatal hyperbilirubinaemia can be made.[21-23] In this study, we tried to find the relationship between umbilical cord blood bilirubin level and risk of neonatal jaundice. The umbilical cord blood bilirubin level estimation is a non-invasive, cheaper and easier method which does not require expertise and difficult machinery, thus can be used to predict neonatal jaundice in rural areas of developing countries like India.

The early prediction of neonatal jaundice has resulted in decline of the complications of this disease. Now-a-days the discharge from hospital after delivery is done within 48 hours. Most of the patients do not return for follow up especially the people living in rural areas. Through this early prediction we can rule out the occurrence of neonatal jaundice and thus decrease the bilirubin-related neurological sequelae.[24,25]

Currently, we do not have a trustworthy technique of anticipating such levels of hyperbilirubinaemia. It is probable that quicker and rapid follow-up after birth and discharge from the hospital might avoid kernicterus development, but rare sporadic cases of kernicterus may not be avertible unless we accept a methodology to scrutiny of the newborn that is substantially less laborious. The feasibility, costs, risks and benefits of such an approach need to be determined.[20,25]

There are certain advantages of using umbilical cord blood collection as a method of prediction. It is an easier and safe method causing no pain to the patient. Since it is a non-invasive method, so causes no risk of maternal and neonatal infection. This method do not prolongs the hospital stay of the patient thus not increasing the financial burden.[26,27]

In a study conducted by Bernaldo et al[21] and Newman et al[28], the prevalence of neonatal jaundice was found to be more in males as compared to females. Similarly in our study, 59.3% of males developed neonatal jaundice as compared to 40.6% of females, but this was not statistically significant.

Phelan et al[29] found the statistical significant correlation between normal vaginal delivery and development of significant jaundice. In contrast to this study, 62.5% of subjects delivered through caesarean section underwent phototherapy whereas only 37.5% subjects delivered vaginally were treated with phototherapy. This difference was found to be statistically significant.

The researches done by Stevenson et al.[30], Newman et al.[28] and Singhal et al.[31] suggested that there is a significant association between jaundice and increasing maternal age. 64% of neonates developed hyperbilirubinaemia whose mother's age was < 25 years, whereas only 19 % of neonates suffered from the disease when maternal age was > 35 years. Thus we can conclude that incidence of jaundice decreases with the increase in maternal age.

The current study suggests a statistical significant relation between increasing umbilical cord blood bilirubin level and development of neonatal jaundice. Various studies suggest that as the umbilical cord bilirubin level increases, the risk of developing hyperbilirubinaemia also increases exponentially.[7,21,26,30] Hence, cord bilirubin can be taken as a valuable indicator of expecting subsequent neonatal hyperbilirubinaemia.

CONCLUSION

This study recommends that cord blood sample should be collected in all term healthy babies born for measurement of cord blood bilirubin and those babies with high cord bilirubin level should not be discharged early as there is the risk of development of jaundice or kernicterus.

REFERENCES

1. Mishra S, Agarwal R, Deorari AK, et al. Jaundice in the newborns. Ind J Paediatr 2008;75(2):157-63.
2. Catz C, Hanson JW, Simpson L, et al. Summary of workshop: early discharge and neonatal hyperbilirubinaemia. Paediatrics 1995;96(4):743-5.
3. Escobar GJ, Braveman PA, Ackerson L, et al. A randomized comparison of home visits and hospital-based group follow-up visits after early postpartum discharge. Paediatrics 2001;108(3):719-27.
4. Radmacher P, Massey C, Adamkin D. Hidden morbidity with successful early discharge. J Perinatol 2002;22(1):15-20.
5. Kiely M, Drum MA, Kessel W. Early discharge risks, benefits and who decides. Clin Perinatol 1998;25(3):539-53, vii-viii.
6. Seidman DS, Stevenson DK, Ergaz Z, et al. Hospital readmission due to neonatal hyperbilirubinaemia. Paediatrics 1995;96(4 pt 1):727-9.
7. Kliegman M, Stanton BF, Geme JW, et al. Nelson textbook of paediatrics. Philadelphia: Saunders Elsevier, 2011;19th ed.
8. Bhutani VK, Schwoebel A, Johnson LH. Serious Adverse events related to neonatal exchange transfusion. J Neonatol 2001;1:32-8.
9. Deorari AK, Agarwal R. Phototherapy units. J Neonatol 2001;1:61-8.
10. Dutta S. Phototherapy for neonatal jaundice-recent advances and controversies. J Neonatol 2001;1(1):39- 44.
11. Cloherty JP, Eichenwald EC, Hansen AR, et al. Manual of neonatal care. Philadelphia: Lippincott Williams & Wilkins, 2012;7th ed.
12. Bahi L, Sharma R, Sharma J. Etiology of neonatal jaundice in Shimla. Indian Paediatr 1994;31(10):1275-8.
13. Murki S, Kumar P, Majumdar S, et al. Risk factors of kernicterus in term babies with non haemolytic jaundice. Indian Paediatr 2001;38(7):757-62.
14. Moyer VA, Ahn C, Sneed S. Accuracy of clinical judgement in neonatal jaundice. Arch Paediatr Adolesc Med 2000;154(4):391-4.
15. Rosenfeld J. Umbilical cord bilirubin levels as a predictor of subsequent hyperbilirubinaemia. J Fam Pract 1986;23:556-8.
16. Knudsen A. Prediction of the development of neonatal jaundice by increased umbilical cord blood bilirubin. Acta paediatr scand 1989;78(2):217-21.
17. Ho NK. Neonatal jaundice a second 4 year experience in toa payoh hospital (1986-1989). J Singapore Paediatr Soc 1991;33(3-4):149-55.
18. Phuapradit W, Chaturachinda K, Auntlamai S. Risk factors for neonatal hyperbilirubinaemia. J Med Assoc Thai 1993;76(8):424-8.
19. Rataj J, Kornacka M, Korman E. Usefulness of measuring bilirubin levels in cord blood for predicting hyperbilirubinaemia in newborns. Ginekol Pol 1994;65(6):276-80.
20. Suchonska B, Wielgos M, Bobrowska K, et al. Concentration of bilirubin in the umbilical blood as indicator of hyperbilirubinaemia in newborns. Ginekol Pol 2004;75(10):749-53.
21. Bernaldo AJ, Segre CA. Bilirubin dosage in cord blood: could it predict neonatal hyperbilirubinaemia? Sao Paulo Med J 2004;122(3):99-103.
22. Knupfer M, Pulzer F, Gebauer C, et al. Predictive value of umbilical cord blood bilirubin for postnatal hyperbilirubinaemia. Acta Paediatr 2005;94(5):581-7.
23. Sun G, Wang YL, Liang JF, et al. Predictive value of umbilical cord blood bilirubin level for subsequent neonatal jaundice. Zhonghua Er Ke Za Zhi 2007;45(11):848-52.
24. Awasthi S, Rehman H. Early prediction of neonatal hyperbilirubinaemia. Indian J Paediatr 1998;65(1):131- 9.
25. Alpay F, Sarici SU, Tosuncuk HD, et al. The value of first day bilirubin measurement in predicting development of significant hyperbilirubinaemia in healthy term newborn. Paediatrics 2000;106(2):e16.
26. Agarwal R, Deorari AK. Unconjugated hyperbilirubinaemia in newborn: current perspective. Indian Paediatr 2002;39:30-42.
27. Randev S, Grower N. Predicting neonatal hyperbilirubinaemia using first day serum bilirubin levels. Indian J Paediatr 2010;77(2):147-50. doi: 10.1007/s12098-009-0335-3.
28. Newman M, Liljestrand P, Escobar GJ. Jaundice noted in the first 24 hours after birth in a managed care organization. Arch Paediatr Adolesc Med 2002;156(12):1244-50.
29. Phelan GJ, Taylor JA, Liu LL, et al. Early newborn hospital discharge and readmission for mild and severe jaundice. Arch Paediatr Adolesc Med 1999;153(12):1283-8.
30. Stevenson DK, Vreman HJ, Wong RJ, et al. Carbon monoxide and bilirubin production in neonates. Semin Perinatol 2001;25(2):85-93.
31. Singhal V, Nutan Kamath, Baliga BS, et al. Cord blood bilirubin level as an early predictor of neonatal hyperbilirubinaemia-a hospital based prospective study. Perinatology 2012;13(1):1-8.