STUDY TO PREDICT NEWBORN AT RISK OF DEVELOPING NEONATAL HYPERBILIRUBINAEMIA BY MEASURING CORD BLOOD BILIRUBIN

Uthaya Kumaran[1], Ajay Kumar Arya[2], Ritu Rakholia[3]

[1]Post Graduate, Department of Paediatrics, Dr. Susheela Tiwari Government Hospital, Haldwani.
[2]Professor & HOD, Department of Paediatrics, Dr. Susheela Tiwari Government Hospital, Haldwani.
[3]Associate Professor, Department of Paediatrics, Dr. Susheela Tiwari Government Hospital, Haldwani.

ABSTRACT

BACKGROUND

NNH is a common problem in neonates during 1st week of life. Early discharge of healthy-term newborn is a common practice and NNH is a cause for readmission in most babies. Our aim was to predict the risk of NNH using cord bilirubin values.

METHODS

Around 150 intramurally delivered healthy term neonates were prospectively enrolled. Cord bilirubin and serum bilirubin at or after 72 hours were estimated.

RESULTS AND DISCUSSION

Using statistical analysis SPSS 19.0.2 program for windows, significant hyperbilirubinaemia was found in 14% of the neonates. Using cord bilirubin >2 mg/dL, significant hyperbilirubinaemia can be predicted with sensitivity of 90.4%, specificity of 75.1%, PPV of 37.2%, NPV of 97.9% and a p value of <0.05.

CONCLUSION

A high NPV in our study suggests that healthy term babies with cord bilirubin <2 mg/dL can be discharged early with assurance to parents.

KEYWORDS

Bilirubin, Hyperbilirubinaemia, Newborn.

HOW TO CITE THIS ARTICLE: Kumaran U, Arya AK, Rakholia R. Study to predict newborn at risk of developing neonatal hyperbilirubinaemia by measuring cord blood bilirubin. J. Evolution Med. Dent. Sci. 2016;5(31):1676-1682,
DOI: 10.14260/jemds/2016/395

INTRODUCTION

Neonatal hyperbilirubinaemia is a cause of concern for the parents as well as for the paediatricians.[1] Early discharge of healthy term new-borns after delivery has become a common practice because of medical and social reasons and economic constraints.[2,3] It is significant that the most common cause for readmission during the early neonatal period is hyperbilirubinaemia.[4,5]

Thus the recognition, follow-up and early treatment of jaundice has become more difficult as a result of earlier discharge from the hospital. Severe jaundice and even kernicterus can occur in some full-term healthy new-borns discharged early with no apparent early findings of haemolysis.[6]

Jaundice in newborn is quite common affecting nearly 60% of term and 80% of preterm neonates during first week of life.[7] The treatment of severe neonatal jaundice by exchange transfusion is costly, time consuming associated with complications and requires skilled manpower.[8]

Financial or Other, Competing Interest: None.
Submission 16-02-2016, Peer Review 22-03-2016,
Acceptance 28-03-2016, Published 18-04-2016.
Corresponding Author:
Uthaya Kumaran,
1/143, Valliammalpuram,
Therkumadathur Post Office,
Alangulam Taluk,
Tirunelveli Dist.,-627423,
Tamilnadu.
E-mail: imuthayakumaran@gmail.com
DOI: 10.14260/jemds/2016/395

Early treatment of jaundice with phototherapy is simple, cheap and effective.[9,10]

The concept of prediction of jaundice offers an option to pick up babies at risk of neonatal hyperbilirubinaemia. A total serum bilirubin of >15 mg/dL is found in 3% of normal term babies.[11] The incidence of hyperbilirubinaemia depends upon ethnic variations, regional variations.[12,13] laboratory variability in measuring serum bilirubin and the incidence of breast feeding.[14] Several investigators have tried to find a simple marker for predicting hyperbilirubinaemia. Some of them used cord bilirubin estimation.[15-23] bilirubin estimation during 6 to 24 hours of life.[24-27] Predischarge hour specific bilirubin estimation.[28] transcutaneous bilirubin measurement.[29-37] and End-Tidal Carbon Monoxide (ETCO) measurement.[38,39] to predict the subsequent development of neonatal jaundice.

There is an obvious need to develop simple predictive guidelines that will enable the physicians to predict or to identify which of the early discharged new-borns will develop significant hyperbilirubinaemia and thereby minimise the risk of bilirubin dependent brain damage.

Our hospital is a tertiary care centre in the Kumaon region of Uttarakhand where most people come from remote hilly areas where people have to walk for six to eight hours to reach their village and adjoining areas of Uttar Pradesh. Followup of those babies who are discharged from our hospital is extremely difficult and hence need a safe cut-off value of umbilical cord bilirubin value below which we can safely discharge the baby.

To the best of our knowledge, there are no studies determining the safe cut-off value of umbilical cord bilirubin level in predicting neonatal hyperbilirubinaemia in Kumaon or Garhwal region of Uttarakhand. A Study in our Kumaon region by Veena Prasad and Nutan Singh.[40] in 2013 concluded that umbilical cord blood can be utilized for estimation of serum bilirubin to predict development of neonatal hyperbilirubinaemia and decide the need for appropriate intervention in neonates, but no cut-off value had been determined. This has created interest in the principal investigator to take up this area of research where knowledge gap exists. This study will give a safe cut-off value of umbilical cord blood bilirubin level, below which we can safely discharge healthy term newborn babies.

AIMS AND OBJECTIVES

To estimate critical cord blood bilirubin level as a predictor of significant hyperbilirubinaemia in healthy new-borns.

METHODS

The study was conducted in Department of Paediatrics, Government Medical College, Haldwani, attached to Dr. Susheela Tiwari, Government Hospital, Haldwani. Initially around 175 healthy term new-borns born in our hospital during the period from October 2014 to May 2015 were enrolled in the study. Our study was a prospective observational study and approved by the Research Ethics Committee of Dr. Susheela Tiwari, Government Hospital, Haldwani.

Inclusion Criteria

- Term babies.
- Birth weight >2.5 kg.
- Apgar >or= 7/10 at 1 min.

Exclusion Criteria

- Sick babies admitted to newborn care unit (Except for phototherapy) including G6PD deficiency.
- Babies whose mother receiving drugs (AEDs, Antimalarials, sulfonamides).
- Prematurity.
- Major congenital anomalies.
- Birth asphyxia (Apgar <7 at 5 min).

Method of Collection of Data

Informed consent was obtained from all the parents of the new-borns to be enrolled for the study. In all the new-borns, relevant information was collected in a predesigned proforma.

- Cord blood was collected in a plain vial at birth for estimation of total bilirubin.
- All enrolled babies were followed up for first 5 postnatal days and clinical assessment for jaundice was done according to Kramer dermal scale.
- 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.

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 azobilirubin with absorbance directly proportional to bilirubin concentration. 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.[41]

Significant jaundice was defined as total serum bilirubin >15 mg/dL, which was considered as hyperbilirubinaemia requiring phototherapy according to AAP guidelines.

Analysis of Data

The data were compiled and entered in MS Excel sheet and the analysis was carried out using the Statistical Package for the Social Sciences (SPSS 19.0.2) program for windows. The critical bilirubin level, measured from the umbilical cord blood having the highest sensitivity, was determined with the Receiver Operating Characteristic (ROC) curve analysis. 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. P values with significance of 0.05 were considered statistically significant. All infants were classified into 4 groups depending on the UCSB levels <1 mg/dL (group-I), 1.1 to 2 mg/dL (group-II), 2.1 to 3 mg/dL (group-III), and >3 mg/dL (group-IV).

RESULTS

Out of total 175 new-borns 25 neonates were excluded from the study and of the remaining 150 new-borns 21 developed significant jaundice. The incidence of significant jaundice requiring phototherapy in our study population is 14% of total new-borns.

Maternal Details	Total		Phototherapy	
	Number	%	Number	%
Age of Mother in Years (P=0.258 Not Significant)				
< 25	92	61.3	15	16.3
26-30	51	34	4	7.8
31-35	6	4	2	33.3
>35	1	0.7	0	0
Order of Birth (P=0.807 Not Significant)				
1	85	56.7	13	15.3
2	51	34	6	11.7
3	11	7.3	2	18.2
4	3	2	0	0
Mode of Delivery (P=1 Not Significant)				
NVD	60	40	8	13.3
LSCS	90	60	13	14.4

Table 1: Maternal Factors and Requirement of Phototherapy

In this study, 60 (40%) were delivered by Normal Vaginal Delivery (NVD) and 90 (60%) by Lower Segment Caesarean Section (LSCS). This may be because most antenatal cases are referred from distant hilly areas to our hospital, which is a tertiary care centre in the Kumaon region of Uttarakhand. The number of infants born by NVD who developed hyperbilirubinaemia were 8 (13.3%) as compared to those who required phototherapy born by LSCS (14.4%) and this was not statistically significant (Table 1).

Details of Neonates	Total		Phototherapy	
	Number	%	Number	%
Sex (P=0.69 Not Significant)				
Male	87	58	16	18.4
Female	63	42	5	7.9
Gestation Weeks (P=0.129 Not Significant)				
37 –39	63	42	12	19
40 –42	87	58	9	10.3
Birth Weight in Kilograms (P=0.855 Not Significant)				
2.50 –2.99	82	54.7	11	13.4
3.00 –3.49	50	33.3	8	16
3.50 –4.00	18	12	2	11.1

Table 2: Neonatal Factors and Requirement of Phototherapy

No significant association between neonatal factors and significant jaundice requiring phototherapy was found in this study (Table 2).

Risk Factors	Total		Phototherapy	
	Number	%	Number	%
Oxytocin Use (P=0.311 Not Significant)				
Yes	8	5.3	2	25
No	142	94.7	19	13.3
Feeds (P=1.000 Not Significant)				
Mother	85	56.7	12	14.1
Both Mother & top feeds	65	43.3	9	13.8
Jaundice in Previous Siblings (P=1.000 Not Significant)				
Yes	8	5.3	1	12.5
No	142	94.7	20	14.1
PIH (P=0.601 Not Significant)				
Yes	8	5.3	0	0
No	142	94.7	21	14.8
Meconium (P=0.632 Not Significant)				
Yes	10	6.7	2	20
No	140	93.3	19	13.6
PROM (P = 0.375 Not Significant)				
Yes	30	20	6	20
No	120	80	15	12.5
Signs of External Bleeding (P=0.008 Highly Significant)				
Yes	7	4.7	4	57.1
No	143	95.3	17	11.9
APH (P = 1.000 Not Significant)				
Yes	2	1.3	0	0
No	148	98.7	21	14.2

Table 3: Maternal Risk Factors and Requirement of Phototherapy

Mothers with risk factors including oxytocin use, jaundice in previous siblings, pregnancy-induced hypertension, meconium stained liquor, premature rupture of membranes, antepartum haemorrhage had no significant association with requirement of phototherapy. Neonates with signs of external bleeding like cephalhaematoma were 7 (4.7%) of which 4 (57.1%) required phototherapy, which was statistically highly significant (P<0.01) (Table 3).

In this study, there was an association found between the blood group of the mother and development of neonatal hyperbilirubinaemia which was statistically significant.

Also neonates born with ABO incompatibility were 34 (22.7%), Rh incompatibility were 3 (2%) of which 14 (41.1%) and 1 (33.3%) required phototherapy respectively, which was statistically significant (P<0.05) (Table 4).

Blood Group	Total		Phototherapy	
	Number	%	Number	%
Mother's Blood Group (P=0.009 Significant)				
A +	36	24	1	2.7
B +	42	28	4	9.5
O +	47	31.3	13	27.7
AB +	20	13.3	2	10
A -	1	0.7	0	0
B -	2	1.3	0	0
O -	1	0.7	0	0
AB -	1	0.7	1	100
Neonates Blood Group (P=0.188 Not Significant)				
A +	57	38	12	21.1
B +	40	26.7	7	17.5
O +	45	30	2	4.4
AB +	5	3.3	0	0
A -	2	1.3	0	0
B -	1	0.7	0	0
O -	0	0	0	0
AB -	0	0	0	0
Incompatibility (P=0.000 Highly Significant)				
ABO	34	22.7	14	41.1
Rh	3	2	1	33.3
No incompatibility	113	75.3	6	5.3

Table 4: Blood Group and Requirement of Phototherapy

Cord Bilirubin in mg/dL	Total		Phototherapy	
	Number	%	Number	%
Association between cord bilirubin and requirement of phototherapy (P<0.05 Significant)				
1st group (<1)	2	1.3	0	0
2nd group (1.1 –2)	97	64.7	2	2.1
3rd group (2.1 –3)	39	26	8	20.5
4th group (>3)	12	8	11	91.7
Association between cord bilirubin and requirement of Phototherapy with taking >2 mg/dL level as cut-off (P<0.05 Significant)				
>2	51	34	19	37.3
<=2	99	66	2	2

Table 5: Predictive Ability of Hyperbilirubinaemia Requiring Phototherapy using Cord Bilirubin Level

Out of total 150 neonates 2 (1.3%) were in Group I (cord bilirubin <1 mg/dL), 97 (64.7%) were in Group II (Cord bilirubin 1.1–2 mg/dL), 39 (26%) were in Group III (Cord bilirubin 2.1 –3 mg/dL) and 12 (8%) neonates were in Group IV (Cord bilirubin >3 mg/dL) (Table 5).

Among 21 new-borns who required phototherapy, majority 11 (52.4%) were in Group IV and none in Group I. There was statistically highly significant (P<.001) association between requirement of phototherapy and increasing cord bilirubin levels. This study shows that number of infants requiring phototherapy proportionately increased as the cord bilirubin increased, i.e. from 2% in Group II to 91.7% in Group IV (Table 5).

With ROC analysis, a mean umbilical cord bilirubin level of >2 mg/dL was determined to have the highest sensitivity and specificity to predict the new-borns who would develop significant hyperbilirubinaemia. In this study, using cord bilirubin level of >2 mg/dL, hyperbilirubinaemia could be predicted with sensitivity of 90.4%, specificity of 75.1%, Positive Predictive Value (PPV) of 37.2% and Negative Predictive Value (NPV) of 97.9%.

At this critical mean serum bilirubin level, the NPV was very high and the PPV was fairly low. Of the 51 new-borns who had a cord bilirubin level of >2 mg/dL, 19 (37.3%) developed significant hyperbilirubinaemia in first 5 days of life, whereas only 2 (2%) of the 99 new-borns who had cord bilirubin level of <2 mg/dL developed significant hyperbilirubinaemia later on. The area under ROC curve is 0.9 (95% CI 0.81 to 0.98, p-value <0.05) when cord bilirubin level of 2 mg/dL was used as a screening test (Graph 1).

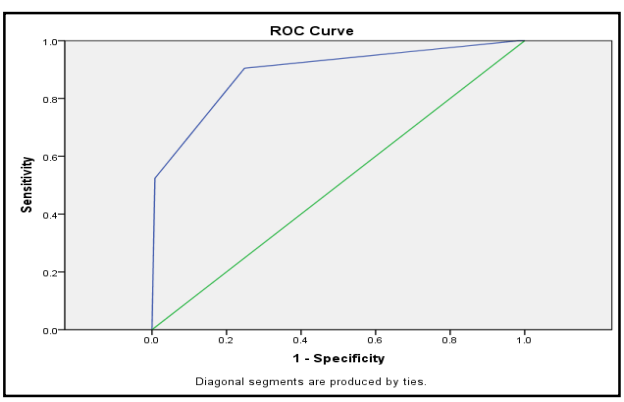

Fig. 1: ROC Curve for Cut-Off Value of the Cord Blood Bilirubin for Prediction of Significant Hyperbilirubinaemia

Cord Bilirubin in mg/dL	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
1.5	95.2	27.13	17.5	97.2
2	90.4	75.1	37.2	97.9
3	52.3	99.2	91.6	92.7

Table 6: Validity and Predictive Values of Cord Bilirubin in Assessing Hyperbilirubinaemia

DISCUSSION

Serum bilirubin levels are usually 1-3 mg/dL at the time of birth and rise at the rate of less than 5 mg/dL/day, peaking at 2–3 days in term neonates. Our study hypothesis 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, because it is a non-invasive way and the result is available within few hours after birth.

The growing practice of early discharge of new-borns has resulted in a re-emergence of bilirubin-related neurological sequelae. Therefore, it is important to establish safe markers to detect babies at risk for significant hyperbilirubinaemia. Development of safe marker will help in preventing fatal outcome due to jaundice. To address this issue, AAP recommends that follow-up should be provided to all neonates discharged less than 48 hours after birth by a health care professional in an office, clinic or at home within 2 to 3 days of discharge. Compliance with this advice may not be easy, however, particularly in rural or lower socio-economic areas and given the rarity of kernicterus it will be very difficult if not possible to document the benefits of this policy.

The experience of mothers in observing infants for the development of jaundice is not satisfactory. Despite such instructions, it is difficult for many parents to recognize significant jaundice.

Currently, we do not have a reliable method of anticipating such levels of hyperbilirubinaemia. It is possible that closer and more frequent follow-up after birth and discharge from the hospital might prevent development of kernicterus, but rare sporadic cases of kernicterus may not be preventable unless we adopt an approach to surveillance of the newborn that is substantially more rigorous than has been practised. The feasibility, costs, risks and benefits of such an approach need to be determined.

Umbilical cord blood collection is not associated with any pain. Furthermore, most important is that the data are available immediately after birth. The babies at risk for developing hyperbilirubinaemia can be detected at birth in a non-invasive way if the neonate leaves the hospital within the first few postnatal days. The use of cord blood bilirubin values may help to predict infants with low risk for hyperbilirubinaemia and minimise an unnecessary prolongation of hospitalization.

Keeping these factors in consideration, our study was conducted on term healthy neonates born in Dr. Susheela Tiwari Government Hospital, Haldwani. The outcome was hyperbilirubinaemia. We have considered peak serum bilirubin level >15 mg/dL at or more than 72 hours of age as significant hyperbilirubinaemia since specific treatment is considered at or above this level.

The prevalence of hyperbilirubinaemia in this study was 14%, which is comparable to 10% to 15% in various other studies.[15,16,20] In a study by Bernaldo AJ, Segre CA.[21] prevalence was 19.86% as no cut-off was mentioned for bilirubin level on third day of life above which phototherapy was required, whereas in a study by Taksande et al.[42] prevalence was 9.5% only because the cut-off for significant hyperbilirubinaemia on 3rd day of life was taken as 17 mg%.

Study	Year	Number of Cases	Hyperbilirubinaemia (%)
Palmer.[43]	1983	41057	10.7
Alpay et al.[25]	2000	498	12.05
Bernaldo AJ.[21]	2004	380	19.86
Knupfer et al.[22]	2005	1100	10.6
Taksande et al.[42]	2005	200	9.5
Zakia et al.[44]	2009	84	15.5
Randev S et al.[27]	2010	200	12

Table 7: Comparison of Prevalence of Hyperbilirubinaemia

Sex ratio in this study was 1.38:1. The prevalence of hyperbilirubinaemia was more in males as compared to females, but this was not found to be significant which is comparable with studies by Bernaldo, Seidman et al. and Newman et al.[21,45,46] (Table 2).

Majority of the deliveries in this study were caesarean sections (60%), while 40% were normal vaginal deliveries and was statistically not significant. This is in agreement to a study done by Suchonska et al. in which no significant relation was found between route of delivery and neonatal hyperbilirubinaemia. However, in a study done by Phelan et al. significant correlation between babies born by normal deliveries and significant jaundice was there.[20,47] (Table 1).

In this study, most infants were first in birth order (85%), but with no significant association between hyperbilirubinaemia and birth order. This is not in similar with the findings of a study by Phelan et al. where primiparous mothers are more likely to have jaundiced infants.[47] (Table 1).

In this study, no significant association was found between maternal age and development of hyperbilirubinaemia in new-borns. This is in agreement with a study done by Srivastav et al.[48] However, studies done by Seidman et al., Newman et al. and Rakesh et al. have found that there is a significant association between jaundice and increasing maternal age.[45,46,49] (Table 1).

The mean cord bilirubin level was 1.93±0.65 mg/dL in the present study and the number of new-borns with significant hyperbilirubinaemia increased with increasing UCSB levels in this study.

Study	Knud-sen.[16] (%)	Knupfer et al.[22] (%)	Taksande et al.[43] (%)	Zakia et al.[44] (%)	Singha IV et al.[50] (%)	Present Study (%)
Cord bilirubin in mg/dL	2.33	1.74	2	2.5	1.9	2
Sensiti-vity	13	97	89.5	77	90	90.4
Specifi-city	99	41.4	85.1	98	82.6	75.1
PPV	85	4.8	38.6	91	45.7	37.2
NPV	72	99.8	98.7	96	98.1	97.9

Table 8: Statistics and Predictive Ability of UCSB

In the present study, UCSB value of 2 mg/dL was considered as cut-off to predict subsequent hyperbilirubinaemia requiring phototherapy in view of an increase in the percentage of neonates developing hyperbilirubinaemia above this value (2.1% –20.5%) between the two groups. With lower cut-off value (As with the study by Knupfer et al.[22]) sensitivity and NPV increases, but specificity and PPV decreases. If a higher cut-off value is considered (As with the study by Knudsen.[16] Zakia et al.[44]) specificity and PPV increases, but sensitivity and NPV decreases. Hence, considering a cut-off of 2 mg/dL in this study has resulted in fairly comparable sensitivity and NPV to that of the study by Knupfer et al. and higher specificity and PPV (Table 8).

Study	Year	Cord Bilirubin in mg/dL	Hyperbilirubinaemia (%)
Knudsen.[16]	1989	< 1.17	2.9
		> 2.34	85
Rataj et al.[19]	1994	< 1	2.4
		> 2.5	89
Bernaldo AJ.[21]	2004	< 2	0
		> 2	53
Knupfer et al.[22]	2005	< 1.17	0
		1.17 –1.75	0.3
		1.75 –2.34	3.4
		> 2.34	8.6
Taksande et al.[43]	2005	< 2	2
		> 2	17
Zakia et al.[44]	2009	< 2.5	4.1
		> 2.5	90.9
Present Study	2015	< 1	0
		1.1 –2	2.1
		2.1 –3	20.5
		> 3	91.7

Table 9: Relationship between Cord Bilirubin and Significant Jaundice

Present study shows that there is significant association between rising cord bilirubin level and development of jaundice in subsequent postnatal days, which is in comparison with other studies (Table 9). As the umbilical cord bilirubin level increases, the risk of developing hyperbilirubinaemia also increases exponentially. Hence, cord bilirubin can be considered as an useful indicator of predicting subsequent neonatal hyperbilirubinaemia and aids in identifying the low risk group children with UCSB level of <2 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 new-borns for evaluating neonatal hyperbilirubinaemia.

To optimize utilization of the limited neonatal care facility available in our country, it is essential to have practical guidelines to predict which new-born would develop significant jaundice and to avoid preventable kernicterus. From the present study, it can be concluded that estimation of cord bilirubin considering the critical bilirubin level of >2 mg/dL at birth will help predict nearly all healthy term new-borns who would have significant jaundice and will require a phototherapy treatment later during first few days of life. It can also be concluded that new-borns with cord bilirubin level of <1 mg/dL are unlikely to have neonatal hyperbilirubinaemia.

Limitations

1. The main limitation of the study was small sample size as the duration of study was only eight months.
2. In this study, preterm babies and low birth weight babies between 1.5 and 2.5 kg were not included. There is a practice that these babies are discharged on day 3 and there is a high chance that these babies may develop jaundice and kernicterus if not followed up.

3. Mothers with both ABO and Rh incompatibility were included in the study, which may produce a bias in the results as the babies born to these mothers are at increased risk of developing jaundice.

CONCLUSION

In our setting, infants having umbilical cord blood bilirubin >2 mg/dL should be followed up strictly either in hospital or at an outpatient department on day 5 if practicable. Infants having TSB <2 mg/dL in cord blood can be discharged early.

Thus, we recommend that cord blood sample should be collected in all term healthy babies born in district and peripheral hospital in the Kumaon region of Uttarakhand for measurement of cord blood bilirubin and those babies with cord bilirubin level less than 2 mg/dL can be safely discharged early on day 2/3 without any risk of further development of jaundice or kernicterus.

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