Predicting Significant Hyperbilirubinemia in Healthy Term New-borns, Using First Day Bilirubin Level

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Abstract: The aim of this study was to determine critical predictive serum bilirubin value on first day (24 hrs) of life which can screen healthy term newborns at risk of developing significant hyperbilirubinemia. This was a prospective study conducted at "Maharaja Yashwant Rao Hospital Indore" between August 2008 and September 2009. Serum bilirubin estimation was done by Van Den Berg method to know total and direct reacting bilirubin. We believe that data from this study could be applied to babies at low risk and specially will help to screen babies who may develop neonatal hyperbilirubinemia (NNHB) inspite ruling out risk factors. This group mainly represent in which hyperbilirubinemia is due to- increased enterohepatic circulation, breast milk jaundice, hypothyroidism, drugs, galactosemia, Crigler-Najjar syndrome, Gilbert syndrome, infection etc.

Keywords: Hyperbilirubinemia, New-borns, Bilirubin Level.

INTRODUCTION

Early detection and proper management of neonatal jaundice is often not adequately stressed. The results of delay in referring such babies to well-equipped centers can be disastrous and can lead to permanent disabilities and life threatening complications [1-3], as the neonate grows-up. Steroids, vitamins and liver tonics have no role in the management of neonatal jaundice, the mainstay of the treatment being photo-therapy and if necessary blood exchange transfusion [4,5].

As percentage of hospital deliveries has significantly increased in last one decade one can expect better chances of timely diagnosis of hyperbilirubinemia in hospital delivered new-borns. But this has not exactly happened. Reason behind it lies in two factors, first is common practice of early discharge of healthy term new-born delivered vaginally, and second one is appearance of peak level of bilirubin on day three today five in a new-borns life.

For early prediction of neonatal hyperbilirubinemia (NNHB) currently we can do

- Exclusion of risk factors
- Routine screening for total serum bilirubin (TSB) level)
- Transcutaneous measurement of bilirubin [6]
- End-tidal carbon monoxide estimation[7]

Out of these, exclusion of risk factors can diagnose cases due to increased hemolysis (Rh-isoimmuniszation, ABO incompatibility, G-6- PD deficiency) but still there is a large group of babies which is not covered.

End-tidal carbon monoxide (CO) estimation before discharge is a good tool but not yet available even in tertiary care centers. It has its own limitations (can detect cases with increased hemolysis but not cases like breast milk jaundice) Transcutaneous measurement of bilirubin is not so accurate due to various factors and though routine screening for serum bilirubin level is best way to diagnose such cases, routine follow up is the main problem. So recently lot of work on serum bilirubin of day one to predict cases of significant NNHB has been done [8-11]. Such studies emphasis for further studies for different ethnic groups and geographical areas and to form individual guidelines.

This study is and has been done to formulate a similar guideline for "early prediction on NNHB by measuring day one bilirubin in healthy.

OBJECTIVES

Objective of this study was to determine critical predictive serum bilirubin value on first day (24 hrs) of life which can screen healthy term newborns at risk of developing significant hyperbilirubinemia and it was done under following headings:

- To select healthy term newborns from MYH postnatal ward and enrol eligible cases for study.
- To do primary investigations and monitor Total Serum Bilirubin(TSB) levels of
- These newborns on day one, three, and five.
- To analyze and determine most suitable bilirubin level on day one which may predict maximum cases with significant NNHB in healthy terms newborns" in our institute (MYH, INDORE).

MATERIALS & METHODS

This was a prospective study conducted at "Maharaja Yashwant Rao Hospital Indore" between August 2008 and September 2009.

All newborns with fulfilling following criteria were included:

- Gestation>37weeks (based on last menstrual period and neonatal assessment by expanded New Ballard score)
- Birth weight>2.500 kg (weighed on an electronic weighing scale, accurate up to 10 grams)
- Absence of major congenital malformations and
- Residing in Indore or a nearby place and whose parents agreed to come for follow-up.

Exclusion criteria

Babies were excluded if there was

- Rh incompatibility
- Positive direct Coomb test(DCT)
- Instrumental vaginal delivery (Forceps or Ventouse)
- Cephalhematoma or sings of bleeding
- Birth asphyxia (Apgar < 5 at five minute) or required intubation > 4 minutes.
- Maternal History of (Antepartum haemorrhage, Pregnancy induced hypertension, primary rupture of membrane, Diabetes mellitus)
- Evidence of hemolysis on peripheral smear,
- Sepsis (Blood culture positive)
- Significant illness requiring NICU admission for > 12 hr
- Serum bilirubin measurement was done initially on first 24+ 6 hrs of life & then repeated on third and fifth day of life

All infant with significant NNHB underwent following investigation in order to exclude known cause of NNHB (sepsis, hemolysis)

- Complete blood and differential with retic count
- PS typing (evidence of hemolysis)
- Blood culture
- Hepatic and renal function tests

New-borns with total serum bilirubin (TSB) >12mg/dl were defined as significant hyperbilirubinemia

Cases with significant hyperbilirubinemia were treated with Phototherapy or exchange transfusion if indicated.

Laboratory investigations were done in hospital pathology lab.

Serum bilirubin estimation was done by Van Den Berg method to know total and direct reacting bilirubin. Serum bilirubin estimation on 1st, 3rd and 5th day of life, new-borns in which serum bilirubin exceeded 12mg/dl were taken as case of significant hyperbirubinemia. These babies were investigated in for the cause of hyperbilirubinemia. A detailed antenatal, natal and postnatal history and thorough physical examination was noted in preform .Cases were excluded if evidence of hemolysis or septicemia was found.

ANTENATAL HISTORY

- Parity of mother
- Jaundice in previous sibiling
- Maternal illness (Diabetes mellitus)
- Medication during pregnancy (OC pills in 1st trimester)

- Toxaemia of pregnancy.
- Blood group of mother

NATAL HISTORY

- Obstructive or Prolonged labour
- Mode of delivery
- Oxytocin induced labour
- Premature rupture of membrane (PROM)

POST-NATAL HISTORY

- Birth asphyxia, RDS
- APGAR score
- Gestation age
- Breast feeding
- Urine and stool frequency
- Day appearance
- History of dullness regurgitation of feeds

Sreum bilirubin was estimated by Malloy and Evelyn 1937 at post graduate Research Lab, Chacha Nehru BAL Chikitsalaya Awam Anusandhan Kendra, Indore (M.P.).

RESULTS

Total 467 babies were studied out of which 52 were lost to follow up. Out of remaining 415 cases 13 were ruled out (septicaemia and evidence of hemolysis on peripheral smear).Thus remaining 402 cases were studied. 57 out of 402 ie 14.2 percent developed significant hyperbilirubinemia ie TSB> 12 gm% on day 1, 3 or 5. (Table1).

Table-1: Bilirubin Levels

Bilirubin level	Frequency	Percentage
<12	345	85.8
>12	57	14.2
Total	402	100

Bilirubin Levels of these 57 cases of significant hyperbilirubinemia were analysed retrospectively, to determine single value of serum bilirubin (TSB) on day one to detect maximum cases.

Table-2: Value of TSB on day1

Bilirubin in 24 hour	Normal (total =345)	percentage	NNHB (total= 57)	percentage
<3	172	49.9	0	0
3.1-4.0	119	34.5	4	7
4.1-5.0	50	14.5	19	33.4
5.1-6.0	04	1.2	17	29.8
>6.1	0	0	17	29.8

As seen in the table 2, 49.9 percent among the normal newborns had a value < 3. Almost 60 percent among the NNHB cases had a value of more than 5 on day 1.

Table-3: Comparing mean TSB among Normal and NNHB

Bilirubin in 24 hours	Frequency (%)	Mean(SD)	SE
Normal	345(85.8)	3.073	0.044
NNHB	57(14.2)	5.418	0.158

As seen in table 3, there is a significant difference ($p<0.05$) between the mean bilirubin levels of the two groups ie normal newborns and those with hyperbilirubinemia.

Further in our analysis we used the levels of Bilirubin on day1 to find out which level can be used as a cut off to predict the development of hyperbilirubinemia.

Table-4: shows the sensitivity and specificity of different levels of bilirubin on day 1

Bilirubin in 24hours	True positive	True negative	False positive	False Negative	Sensitivity %	Specificity %
3.0	57	172	173	0	100	49.8
3.5	54	261	3	84	94.74	75.65
4.0	53	288	4	53	92.98	83.48
4.5	50	325	7	20	87.72	94.2
5.0	35	340	22	05	61.40	98.50
5.5	22	345	35	0	38.60	100

As seen in the table 4, the TSB level has a good sensitivity and specificity between 3.5mg/dl and 4mg/dl. Further analysis with the help of ROC curve (Fig.1) indicated that a level of 3.8mg/dl is the precise predictor of neonatal hyperbilirubinemia.
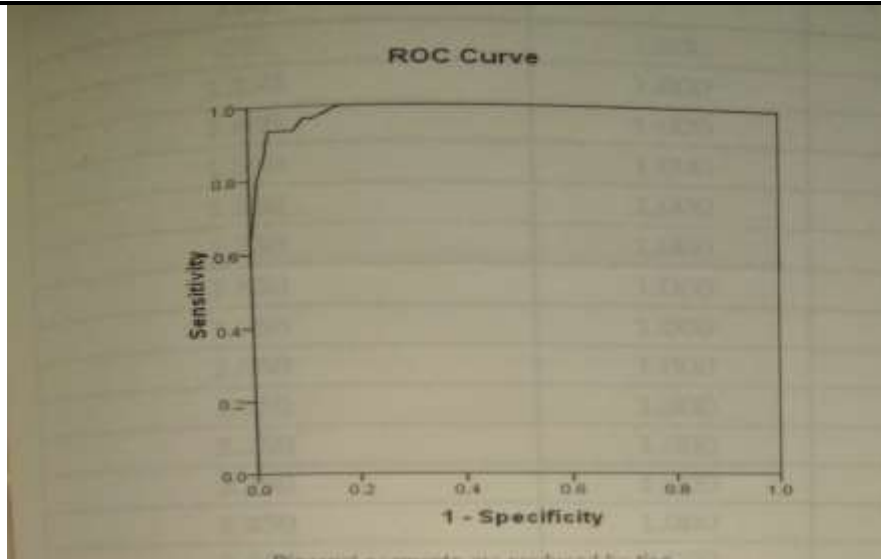
Fig-1: ROC Curve

DISCUSSION

Although there has been a decrease in the length of post-delivery hospital stays for new-borns and their mothers in recent years, there is still much controversy about when, early (<48 hours after delivery) or late (>72 hours after delivery), a mother-child dyad should be discharged [13]. Opponents of the early discharge suggest that various risks, such as hyperbilirubinemia; breast-feeding difficulties and feeding problems leading to dehydration and malnutrition, screening and identification of congenital anomalies, new-born cognitive deficits are missed and may lead to readmission [14]. In contrast, proponents of the early discharge regard it as safe and advantageous because of various medical, social, and economic reasons.

An influencing effect of early discharge on morbidity and mortality of the new-borns has not been established yet, and first studies have not demonstrated any adverse outcomes or any increased readmission risks of early discharge, more recent studies suggest that new-borns discharged early are at increased risk for rehospitalisation during the neonatal period. The current guidelines of American Academy of Paediatrics in western countries, recommend a follow-up for new-borns discharged before 48 hours of life at 2 to 3 days postnatally. However, in our country a complete follow-up is not always possible because of the patient incompliance and lack of medical facilities in peripheral areas thus, there is a need to identify new-borns that are at risk for developing significant hyperbilirubinemia as early as possible.

We aimed, in this study, to prospectively determine the critical serum total bilirubin level to predict significant hyperbilirubinemia in healthy term new-borns based on serum bilirubin measurements at 24 hours of life.

The incidence of significant hyperbilirubinemia depends on regional variations, ethnic makeup of the population, laboratory variability in the measurement of bilirubin, In our study group, there were no significant differences between the cases who did and the cases who did not develop significant hyperbilirubinemia with respect to these and other factors (such as haemoglobin level, gender, delivery route, birth weight, gestational age, and and the incidence of breastfeeding [19] that may be associated with the risk of hyperbilirubinemia.

In 4 studies [8-12] from 3 different countries investigating the predictive value of first-day serum bilirubin measurement on predicting the later development of significant hyperbilirubinemia, the incidence of significant hyperbilirubinemia has been reported to be between 1.7% and 12%.20-23.

The 57 cases with significant hyperbilirubinemia in our study group of 402 newborns represented an incidence of 14.2%. These differences may be attributable to ethnic and geographic variations in different populations (studies have suggested higher incidence of NNHB in Asian population). 23 In our study, the cases that developed significant hyperbilirubinemia also had significantly higher bilirubin levels on days 3 addition to the first-day values, compared with cases that did not develop significant hyperbilirubinemia.

Bhutani *et al*. [8] have prospectively followed term new-borns over the first 5 days of life by measuring serum bilirubin levels daily. In their series of 1097 new-borns, no baby who had a bilirubin level of <5 mg/dL at 20 to 28 hours of life developed significant hyperbilirubinemia (17 mg/dL), whereas 33% of those whose serum bilirubin level at the same hours was at least 8 mg/dL developed significant hyperbilirubinemia. In our study, of the 206 new-borns who had a bilirubin

level of 6 mg/dL in the first 24 hours of life, 26.21% developed significant hyperbilirubinemia, whereas only 2.05% of the 292 new-borns whose bilirubin level was <6 mg/dL on the first day of life developed significant hyperbilirubinemia.

In a similar study by Seidman et al(10), the risk of significant hyperbilirubinemia was 1.6% in cases whose bilirubin level was <5 mg/dL at 24 hours of life, whereas that risk was 6.6% in cases whose bilirubin level was 5 mg/dL at 24 hours of life. In their series of 1075 new-borns, this critical bilirubin level (5 mg/dL) was reported to have a high specificity (91.9%) and a low sensitivity (45.5%) for detecting significant hyperbilirubinemia; the positive predictive value was very low (8.9%) and the negative predictive value was very high (99.0%). Later Alpay, *et al.* [11] reported that TSB levels of 36 mg/dl in the first 24 hr predicted jaundice in all newborns subsequently.

Awasthi, *et al.* [12] showed that TSB level of 3.99 mg/dl at 18-24 hr was able to predict subsequent hyperbilirubinemia (>15 mg/dl) with sensitivity and specificity of 67% each [11]. However, this study had major flaws. Complete follow up was present in infants who stayed in the hospital either for neonatal illness or some maternal reason, such as cesarean section. More than 50% of infants, who were healthy thus discharged early, were not followed up.

In our study, the bilirubin level of 3.8 mg/dL(obtained by ROC), on the first day had the highest sensitivity (94.74%), and very high negative predictive value (98.86%). According to our findings, a critical cut off level of 3.8 mg/dL in the first 24 hours of life predicted 94.74% of the new-borns who developed jaundice. However, the bilirubin level of <3.8 mg/dL did not

Completely exclude the development of significant hyperbilirubinemia; only 1.1% of the new-borns with bilirubin levels of < 3.8 mg/dL developed jaundice and none of them needed a phototherapy. A 98.86% negative predictive value in the present study suggests that measurement of serum bilirubin in the first 24 hours of life can help to identify those new-borns that are unlikely to require further evaluation and intervention. Furthermore, because no cases with a serum bilirubin level of <3.8 mg/dL in the first 24 hours of life required a subsequent phototherapy treatment and because all of those infants requiring a phototherapy treatment were just among the cases whose first-day bilirubin levels were > 3.8 mg/dL, thus critical bilirubin level of 3.8 mg/dL on the first day made it possible, with the highest (100%) sensitivity and negative predictive value, to definitely predict all the infants who would be requiring a phototherapy treatment later in the first days of life.

TSB 3mg/dl has higest sensitivity (100%) while TSB 5.5mg/dl has highest specificity to predict significant NNHB. That means babies with

TSB < 3 mg/dl at 24 + 6 hr were in a no risk zone as none of them developed significant NNHB. Similarly TSB level 6.0 mg/dl at24 + 6 hr

Pre. Here we noticed that so we can devide all babies in three categories
- No risk: TSB < 3 mg/dl
- Low risk: TSB 3 - 6 mg/dl
- High risk: TSB > 6 mg/dl

Based on above we may formulate guidelines for further follow up and management of Babies.

Risk factors which were significantly associated with increased risk of NNHB in our study are gender, mode of delivery, breast feeding and Hb level of new-born .Though other factors like LsCs delivery, meconium not passed up to 24 hours were also associated with increased risk of NNHB in our study but were not significant statistically. While maternal age, maternal Hb was not associated with increased risk of NNHB in our study.

Results from the present study are consistent with previous studies. We found that it was possible to identify infants early who are at high risk and more importantly, those who are at low risk of subsequent hyperbilirubinemia.

CONCLUSION
Our study population included healthy term babies not in high risk group (Rh and ABO hemolysis, G-6-PD def, DM in mother, Cephalhematoma etc) .Nearly all infants were advised exclusively breastfed but top feeding was given to babies when breast feeding was not possible. Complete follow up for at least five days was recorded for 88.6% babies. We believe that data from this study could be applied to babies at low risk and specially will help to screen babies who may develop NNHB inspite ruling out risk factors. This group mainly represent in which hyperbilirubinemia is due to- increased enterohepatic circulation, breast milk jaundice, hypothyroidism, drugs, galactosemia, Crigler-Najjar syndrome, Gilbert syndrome, infection etc. In near future with evolving technology and new advances some more factors responsible for hyperbilirubinemia might fill the gap which we currently term as idiopathic group. In a previous study in our hospital percentage of idiopathic NNHB was 31.6%, so this study could of great help in such babies.

To target limited health care resources more effectively toward high risk newborns. In the era of early discharge of newborns from hospitals, there is an

obvious need to develop practical guidelines to predict which newborns will develop significant hyperbilirubinemia or will require further and close follow-up or intervention. From our particular experience, we conclude that a serum bilirubin measurement and the use of the critical bilirubin level of 3.8 mg/dl in the first 24 hours of life will predict nearly all healthy term newborns who will have significant hyperbilirubinemia and will determine all of those infants who will require a phototherapy treatment later during first days of life. However, results of the present study are applicable only to healthy term newborns, and further studies including larger numbers of newborns should be conducted to establish more sensitive and more predictive guidelines.

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