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Rebound hyperbilirubinemia in newborns more than 35 weeks of gestational age at tertiary care center: a descriptive study

Bijesh Shrestha[1], Anil Raj Ojha[2], Shiva Prasad Sharma Chalise[2]

[1]Lecturer, [2]Assoc. Prof., Dept. of Pediatrics, Patan Hospital, Patan Academy of Health Sciences, Lalitpur, Nepal

Abstract

Introduction: Rebound hyperbilirubinemia is defined as a total serum bilirubin (TSB) value sent following stopping of phototherapy that requires reinstitution of phototherapy. Identification of the risk factors for rebound hyperbilirubinemia facilitates early discharge of newborns without risk factors.

Method: This was a hospital based prospective observational study conducted in a tertiary care centre of Nepal and included 71 newborns born ≥35 weeks of gestational age requiring phototherapy for neonatal jaundice between October 2019 to October 2020. Following complete examination, phototherapy was started and stopped on the basis of threshold graphs of National Institution for Health Care and Excellence (NICE). A rebound TSB was measured 12 hours after stopping phototherapy. A rebound TSB value requiring phototherapy was considered significant. Risk factors like sex, age at onset of jaundice, sepsis, blood group incompatibilities were studied. Data entry and analysis were done using Epi info 7 and Easy R software.

Result: Out of total 71 cases, significant rebound hyperbiliubinemia was found in 15.49%. The cases with rebound had male predominace (81.81%), 54% developed jaundice before 72 hours of life, 28.5% had ABO setting and 21.40% had sepsis. The median difference in TSB value from threshold value at initiation and stoppage of phototherapy for rebound cases were 3.50 and 3.80 respectively.

Conclusion: Rebound hyperbilirubinemia should be assessed in those babies with risk factors and other babies may be discharged without measuring rebound TSB and rather be called for early follow up.

Keywords: Hyperbilirubinemia; Phototherapy; Rebound; Newborns

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Correspondence: Dr. Bijesh Shrestha, Dept. of Pediatrics, Patan Hospital, Patan Academy of Health Sciences, Lalitpur, Nepal,
Email: drbijeshshrestha11@gmail.com

Introduction

Neonatal hyperbilirubinemia is one of the most common conditions seen in 80% of the preterm and 60% of the term newborns in the first week of their lives. It can be objectively diagnosed by measurement of Total serum bilirubin (TSB) or Transcutaneous bilirubin (TcB).[1,2]

Phototherapy converts bilirubin to products that can bypass conjugating system of liver and be excreted in the bile or urine without further metabolism. Both American Academy of Pediatrics and National Institution for Health Care and Excellence (NICE) have developed age wise hour specific serum bilirubin threshold graphs for management of neonatal jaundice.[4,5]

TSB can be repeated 12 to 72 hours after stopping phototherapy in order to check for rebound increase in bilirubin as the underlying alteration in bilirubin production and excretion may persist even following phototherapy.[6] A rebound TSB level that requires the reinstitution of phototherapy is considered significant.[7]

Wide variation in the prevalence of rebound hyperbilirubinemia has been found in different studies conducted worldwide ranging from 4.6% to 24.9%.[8,9] However, literatures regarding the incidence and risk factors of rebound hyperbilirubinemia in Nepal is limited.

Common risk factors associated with rebound are blood group incompatibilities, sepsis, prematurity and early age of jaundice, TSB value at initiation and stopping of phototherapy. [9,11,13]

The importance of incidence and risk factors of rebound hyperbilirubinemia in Nepalese newborns would help us guide monitoring and follow up of neonates requiring phototherapy.

This study was carried out with the aim of finding out the status of rebound hyperbilirubinemia in our setting and study its risk factors so as to facilitate early discharge in those without risk factors.

Method

This is a prospective observational study conducted from October 2019 to October 2020 in the Neonatal unit of Patan Academy of Health Sciences (PAHS) after the approval from the Institutional Review Committee of PAHS (Ref.: PMP1911221307).

All newborns born at ≥35 weeks of gestational age admitted to the neonatal units with neonatal jaundice requiring phototherapy who consent to enroll in the study were included. Newborns with direct serum bilirubin >1 mg/dl (or >15% of TSB) and those requiring exchange transfusion were excluded.[3] A sample size of 71 was included in the study.

Upon receiving a case that fulfilled the inclusion criteria, written informed consent was obtained from the parents. Data collection was conducted through patient examination, chart review, and completion of a structured proforma covering demographic parameters (such as sex and gestational age) and variables including the blood group of the mother and baby, age at onset of jaundice, TSB levels at initiation and cessation of phototherapy, presence of sepsis, feeding practices, and presence of cephalhematoma.

Continuous phototherapy was given except during periods of feeding and nursing care. Phototherapy was stopped when TSB fell at least 2 mg/dl below the threshold level at which phototherapy would be indicated for that age as per the proper age specific graphs.[5,11]

After stopping phototherapy, the babies were kept for observation and rebound total serum bilirubin was measured 12 hours after stopping phototherapy.[5] Significant rebound hyperbilirubinemia was defined as post phototherapy TSB level needing reinstitution of phototherapy.[12] Phototherapy was restarted in such babies. Other babies in whom either the rebound TSB value decreased or increased but less the phototherapy threshold level were not considered significant.

Data were collected in a pre-designed proforma; entry and analysis were done using Epi-Info and Easy R software. Descriptive analysis was done using Median, percentage and presented as tables and figures.

Result

A total of 80 cases were enrolled in the study but three required exchange transfusion, two left against medical advice (LAMA). In two cases phototherapy was stopped earlier and two cases were discharged prior to rebound TSB estimation. So, 71 cases were included in the study. Out of the total 71 cases, 45(63.33%) were males and 26(36.61%) cases were female and 33(46.47%) of babies were between 35 to 37^{+6} weeks of gestation. Onset of jaundice was before 72 hours of age in 40(56.33%) cases and remaining 31(43.66%) had beyond 72 hours of age. Twenty-nine (40.84%) babies were breast fed, 13(18.30%) were formula fed, 26(36.61%) were receiving mixed feeding

Table 1. Frequencies of parameters studied in babies needing phototherapy (N=71)

SN	Parameters		N(%)
1	Sex	Male	45 (0.6333%)
		Female	26 (0.3661%)
2	Gestational Age	35-37+6wk	33 (0.4647%)
		38-39+6wk	25 (0.3521%)
		>=40wk	13 (0.183%)
3	Age at onset of jaundice	<72 hours	40 (0.5633%)
		>= 72 hours	31 (0.4366%)
4	Feeding practice	Breast milk	29 (0.4084%)
		Formula	13 (0.183%)
		Mixed	26 (0.3661%)
		NPO	3 (0.0422%)
5	ABO setting		21 (0.2957%)
6	Rh setting		11 (0.1549%)
7	Sepsis		28 (0.3943%)
8	Cephalhematoma		2 (0.0281%)

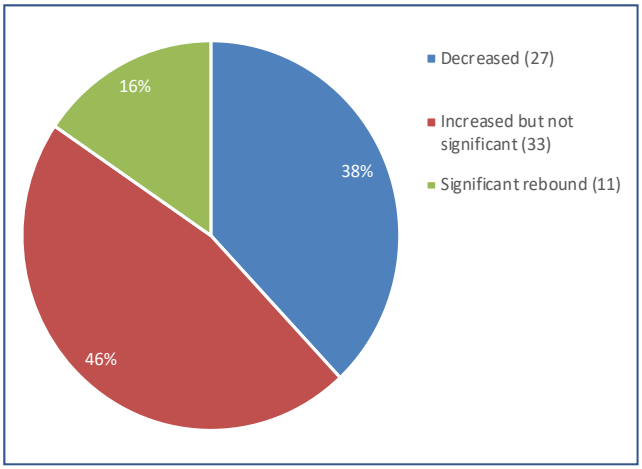

Figure 1. Distribution of rebound TSB post phototherapy

Table 2. Relationship of significant rebound hyperbilirubinemia with various risk factors

SN	Parameters		Rebound Hyperbilirubinemia		Total
			Yes	No	
1	Sex	Female	2(7.69%)	24(92.31%)	26(100%)
		Male	9(20%)	36(80%)	45(100%)
2	Gestational Age	35-37^{+6}wk	5(15.15%)	28(84.85%)	33(100%)
		38-39^{+6}wk	5(20%)	20(80%)	25(100%)
		>=40 wk	1(7.69%)	12(92.31%)	13(100%)
3	Age at onset of jaundice	<72 hours	6(15%)	34(84%)	40(100%)
		>=72 hours	5(16.13%)	26(83.87%)	31(100%)
4	ABO setting	Present	6(28.57%)	15(71.43%	21(100%)
		Absent	5(10%)	45(90%)	50(100%)
5	Rh setting	Present	0(0%)	11(100%)	11(100%)
		Absent	11(18.33%)	49(81.67%)	60(100%)
6	Sepsis	Present	6(21.43%)	22(78.57%)	28(100%)
		Absent	5(11.63%)	38(88.37%)	43(100%)
7	Cephalhematoma	Present	1(50%)	1(50%)	2(100%)
		Absent	10(14.49%)	59(85.51%)	69(100%)
	Total		**11(15.5%)**	**60(84.5%)**	**71(100%)**

Table 3. Median difference of TSB value from threshold at initiation and stopping of phototherapy

Median difference of TSB value from threshold value at	Cases with rebound	Cases with no rebound
Initiation of phototherapy	95% CI 3.50(2-2.95)	95% CI 1.30(0.60-2.60)
Stopping of phototherapy	95% CI 3.80(2.90-5.10)	95% CI 5.65(4.20-8.17)

and three (4.22%) cases were kept Nil per oral. There were 21(29.57%) cases with ABO setting, 11(15.49%) with Rh setting, 28(39.43%) with sepsis and 2(2.81%) with cephalhematoma, Table 1.

Out of the total 71 cases, 11(15.49%) had significant rebound hyperbilirubinemia meaning those cases needed reinstitution of phototherapy, Figure 1. In 27(38%) cases, there was decrease in the rebound TSB value than that was at the time of stopping of phototherapy. In remaining 33(46%) cases, there was increase in rebound TSB value than that was at the time of stopping of phototherapy . However, the rebound TSB was not high enough to restart phototherapy so the rebound TSB was not considered significant.

Among the risk factors studied nine (20%) males and two (7.69%) females had rebound. Similarly, six

(15%) had onset of jaundice before 72 hours and five (16.13%) had onset of jaundice before 72 hours of age. Of the cases with ABO setting, six (28.57%) had rebound but none with Rh setting had rebound and six (21.43%) of babies with neonatal sepsis had rebound, Table 2.

Cases with a very high TSB value at initiation of phototherapy with a median value 3.50(2-5.95) from the threshold value and in whom phototherapy was stopped at a higher value with a median value 3.80(2.90-5.10) below the threshold value had rebound hyperbilirubinemia, Table 3.

Discussion

This study was done to study significant rebound hyperbilirubinemia in 71 babies requiring phototherapy. In the present study, significant rebound hyperbilirubinemia was found to be 15.49%. There have been wide variations in the prevalence of rebound in different studies carried out in different parts of the world. In a retrospective study carried out in the USA including 7048 newborns less than 39 weeks requiring phototherapy, 4.60% of the cases had rebound hyperbilirubinemia but rebound was sent till 72 hours post phototherapy.[8] It had a very large sample size and variability in the time of sending rebound. But it was 9.1% in a similar study done in Turkey and in a study in Israel, 30(13.30%) neonates developed rebound hyperbilirubinemia but only 22 required phototherapy.[13,15] However, in the study published in the year 2018 conducted over 500 newborns, the prevalence was 24.90%.[16] This high prevalence could be attributed to inclusion of preterm babies in the study and prematurity has been shown to be a risk factor for rebound hyperbilirubinemia with statistical significance (p value=0.030).[16]

In our study, there was a male predominance of cases with male: female ratio of 1.7:1. Male sex is considered as the minor risk factor for neonatal jaundice by American Academy of Pediatrics.[4] Similar finding was seen in a study done in Nepal on causes of neonatal jaundice withmale sex as a statistically significant cause for neonatal jaundice with p value <0.001.[17] With regard to rebound hyperbilirubinemia male:female ratio was 4.5:1.

With respect to the gestational age of the babies with neonatal jaundice 33(46.4%) cases were between 35 to 37 weeks of gestation and remaining were between 38 to 39 weeks or more . The AAP considers gestational age as a risk factor for neonatal hyperbilirubinemia and gestational age between 35 to 37 weeks as a major risk factor and between 38 to 39 weeks as a minor risk factor which is consistent with our study.[13]

This study tried to calculate median TSB value difference from threshold value during initiation and stopping of phototherapy which showed that higher TSB level from threshold TSB at initiation of phototherapy had an increased risk of rebound hyperbilirubinemia But lower the TSB level from threshold TSB at stopping of phototherapy showed a decreased risk of rebound hyperbilirubinemia. Other studies also showed higher TSB at initiation of phototherapy and stopping of phototherapy with respect to the threshold TSB value were associated with increased risk of rebound hyperbilirubinemia.[8,9,15]

In this study, out of the cases with ABO setting 28.57% had rebound but none with Rh setting had rebound and 21.48% of the cases with sepsis had rebound. There were only 2 cases with cephalhematoma and one of them had rebound. In the study conducted in India, the incidence of rebound was found to be 12% with prematurity(p<0.01), ABO(p<0.001) and Rh incompatibility(p<0.005), onset of jaundice <72 hours of life (<0.001) as the risk factors for rebound.[11] Sepsis and extravasation of blood like cephalhematoma did not have significant risk of developing rebound.[11] Most other studies have found hemolytic causes like ABO incompatibility, Rh isoimmunization as the significant risk factors for rebound hyperbilirubinemia.[9,13,15] The practice in our hospital regarding management of babies born to Rh negative mothers is more intense and if there is Rh setting then TSB is monitored regularly at least till 48 hours even if there is no jaundice. And if TSB falls in phototherapy range at some point, phototherapy is started early usually at a lower TSB level. Because relation of TSB at initiation of phototherapy with rebound has been shown to be significant, there could be lesser risk of rebound if phototherapy is started at a low TSB level. But ABO setting is identified usually after the baby becomes icteric. Studies done in India and Israel have found sepsis as a statistically significant risk factor associated with rebound.[6,19] The variation in the results could be due the sepsis definition undertaken as not all sepsis considered are culture positive and even suspected sepsis could been taken into account as sepsis.In this study also suspected sepsis cases have been included.

Conclusion

Rebound hyperbilirubinemia is a known phenomenon following phototherapy occurring as a result of ongoing alteration in the bilirubin production and excretion Blood group incompatibilities, sepsis, age at onset of jaundice and high TSB level at initiation and stopping of phototherapy are some of the established risk factors in babies developing rebound hyperbilirubinemia following phototherapy. Assessment for rebound hyperbilirubinemia should be done especially in those babies with risk factors.

Conflict of Interest
None

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None

Author Contribution
Concept, design, planning: BS, ARO, SPSC; Literature review: BS; Data collection: BS; Data analysis: BS, ARO, SPSC; Draft manuscript: BS, ARO, SPSC; Revision of draft: BS; Final manuscript: BS, ARO, SPSC; Accountability of the work: BS, ARO, SPSC.

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