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Original Research Article

Post phototherapy bilirubin rebound: incidence and risk factors

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ABSTRACT

Background: Rebound hyperbilirubinemia may occur after cessation of phototherapy in new-borns in certain high-risk situations. However, data regarding the phenomenon of bilirubin rebound is lacking from India. Aim was to study the incidence and associated risk factors of post phototherapy rebound hyperbilirubinemia.
Methods: The study subjects included all neonates (gestation >34 weeks) admitted to newborn unit who required phototherapy for hyperbilirubinemia. Unit protocol based on American academy of pediatrics (AAP) guidelines were used to start and stop phototherapy. Rebound bilirubin was measured 24±6 hours after stopping phototherapy. Significant bilirubin rebound (SBR) was defined as post phototherapy bilirubin level needing reinstitution of phototherapy. The risk factors associated with significant rebound were studied.
Results: Out of total 509 neonates who received phototherapy due to hyperbilirubinemia, 63 (12%) had significant bilirubin rebound requiring reinstitution of phototherapy. There was significant risk for rebound in neonates who had prematurity ($p < 0.01$), ABO (<0.001) and Rh incompatibility ($p<0.005$) with mother, G6PD deficiency ($p < 0.001$) and onset of hyperbilirubinemia less than 72 hours of postnatal age ($p< 0.001$). However, neonates with extravasations of blood, polycythaemia, sepsis, other causes of haemolysis and idiopathic group did not have significant risk of developing rebound.
Conclusions: Post phototherapy bilirubin estimation and follow up should be ensured in high-risk neonates.

Keywords: Hyperbilirubinemia, Phototherapy, Rebound

INTRODUCTION

Significant bilirubin rebound (SBR) after intensive phototherapy is a cause for readmission in certain clinical situations. It is the result of continued underlying alterations in bilirubin metabolism once serum total bilirubin (STB) levels have fallen below the threshold for treatment. However, these alterations in bilirubin metabolism may persist and because bilirubin rebound after stopping phototherapy, cause conventional thought is that all neonates must have a repeat serum bilirubin level estimation 24 hour (12 to 36 hours) after stopping of phototherapy.[1,2] This had been under scrutiny since long. As many clinicians had observed a low rate of rebound during their practice and have found it optional to measure it routinely.[3-8] Neonatal hyperbilirubinemia, a common morbidity among neonates though well studied, data about the phenomenon of bilirubin rebound is lacking from India.[9] This study aimed to determine the incidence of rebound hyperbilirubinemia and risk factors associated with it.

METHODS

This hospital based prospective study was conducted between June 2013 and May 2014 at neonatal units of

Indira Gandhi medical college, Shimla, Himachal Pradesh, India. All hospitalized neonates (>34 weeks gestation) in newborn units with >72 hours hospital stay suffering from neonatal hyperbilirubinemia requiring phototherapy were study subjects. Newborns with gestation <34 weeks, direct hyperbilirubinemia, prolonged jaundice and hyperbilirubinemia requiring exchange transfusion were excluded. The decision to initiate phototherapy was uniform and in accordance with the unit protocol, based on American academy of pediatrics, clinical practice guidelines 2004 (Figure 1).[10]

Phototherapy was stopped when TSB level fell below 2 mg/dl lower than the phototherapy threshold for that postnatal age. Serum bilirubin was estimated after 24±6 hours of discontinuation of phototherapy. Significant bilirubin rebound (SBR) was defined as post-phototherapy bilirubin level needing reinstitution of phototherapy. Estimation of bilirubin was done by Diazo method of Pearlman and Lee on auto analyzer (Transasia biomedical).

Neonates were routinely evaluated for the following etiological entities for hyperbilirubinemia using clinical data or employing standard laboratory tests: direct Coombs positive/negative ABO and Rh blood group incompatibility, G-6-PD deficiency, sepsis, prematurity (gestational age < 37 weeks), extravasation of blood, polycythemia and breast feeding. Complete hemogram, including reticulocyte count and peripheral blood smear examination was done in all the cases. Thyroid function tests, sepsis screen and blood culture was done, wherever indicated. Data entry and analysis were done using Epi info 7 software and was analyzed by using chi-square or Fisher exact test. P value of <0.05 was considered significant.

RESULTS

During the study period 556 neonates developed significant hyperbilirubinemia requiring phototherapy but 509 (8%) fulfilled the inclusion criteria and constituted the study cohort. Among these 295 (58%) were male and 214 (42%) female.

Etiology of hyperbilirubinemia included: prematurity 106 (21 %), sepsis 76 (15%), ABO incompatibility 60 (12%), Rh incompatibility 47 (9%), other causes of hemolysis 42 (8%), Breast feeding 35 (7%) Extravasation of blood 32 (6%), G6PD deficiency 18 (4%), delayed passage of meconium 11 (2%), polycythemia 9 (2%) and idiopathic in 73 (14 %) newborns (Table 1, Figure 2).

Table 1: Causes of unconjugated hyperbilirubinemia (n = 509) and rebound (n=63).

Causes of hyperbilirubinemia	Number of cases (%)	Rebound (% of causes)	X^2	P value	OR (95% CI)
Prematurity	106 (21%)	21 (20%)	6.82	0.009<0.01	2.12 (1.19-3.77)
Sepsis	76 (15%)	3 (4%)	5.85	0.16	0.26 (0.08-0.84)
ABO incompatibility	60 (12%)	15 (25%)	9.99	<0.001	2.78 (1.44-5.36)
Rh incompatibility	47 (9 %)	12 (26%)	8.26	0.004<0.005	2.76 (1.35-5.66)
Other causes of haemolysis	42 (8%)	2 (5%)	2.45	0.12	0.33 (0.07-1.41)
Breast feeding	35 (7%)	00			
Extravasation of blood	32 (6 %)	03 (9 %)	0.28	0.59	0.72 (0.21-2.43)
G6PD deficiency	18 (4%)	07 (39%)	12.09	< 0.001	4.94 (1.84-13.27)
Delayed passage of meconium	11 (2%)	00 --	--	--	--
Polycythaemia	9 (2%)	00 --	--	--	--
Idiopathic	73 (14%)	00	--	--	--

Table 2: Age of onset of hyperbilirubinemia and rebound.

Onset of hyperbilirubinemia	Number of cases (%)	Rebound (%)	X2	P value	OR (95% CI)
< 72 hours of age	294 (57.8)	49 (16.7%)	11.81	< 0.001	2.87 (1.54-5.35)
72 hours or more of age	215 (42.2%)	14 (6.5%)			
Total	509 (100%)	63 (12.3%)			

Out of 509 neonates needing phototherapy a total of 63 (12%) neonates developed significant bilirubin rebound (SBR) after 24±6 hours of stopping phototherapy. In newborns with SBR, the mean bilirubin increased by 3.1 mg/dl (range; 2.2-4.5 mg/dl) after stopping phototherapy. Of all the newborns with rebound, 21 (33%) were preterm and 42 (67%) term. reflecting significant risk for rebound in preterm versus term neonates (Table 2 and Figure 3).

The number of neonates rebounding in each etiological subgroup were prematurity (21/106), ABO

incompatibility (15/60), Rh incompatibility (12/47), G6PD deficiency (7/18), other causes for hemolysis (2/42), extravasation of blood (3/32) and sepsis (3/76).

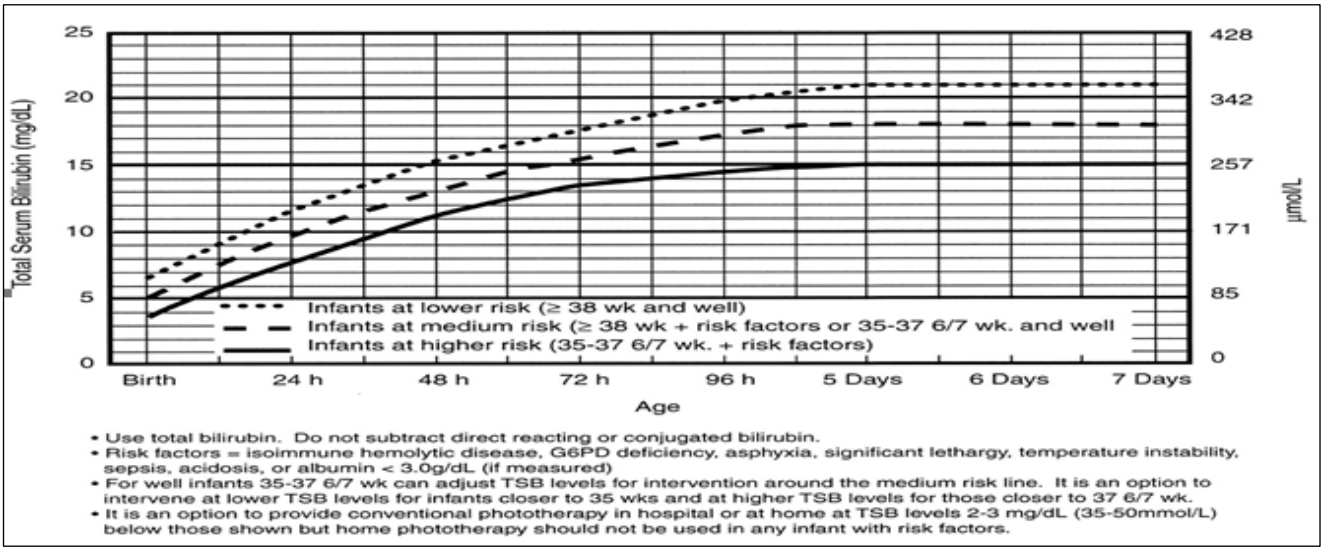

Figure 1: Guidelines for phototherapy in hospitalized infants of 35 or more weeks 'gestation.

The number of neonates rebounding in each etiological subgroup was compared using Epi-info 7 software, taking one factor at a time. Some of the newborns had more than one risk factor for developing rebound hyperbilirubinemia; however multivariate analysis could not be attempted due to less number of neonates.

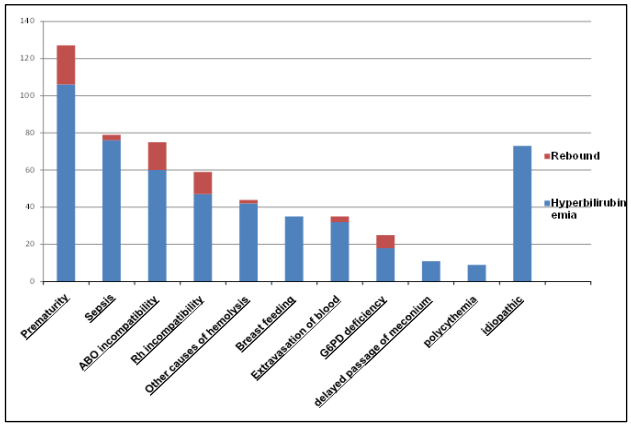

Figure 2: Causes of hyperbilirubinemia (n=509) and rebound (n=63).

There was significant risk for rebound in neonates who had prematurity, ABO and Rh incompatibility with mother, G6PD deficiency and onset of hyperbilirubinemia less than 72 hours of postnatal age (Table 1 and 2).

Interestingly neonates with extravasations of blood, polycythemia, sepsis, other causes of hemolysis and idiopathic group did not have significant risk of developing rebound.

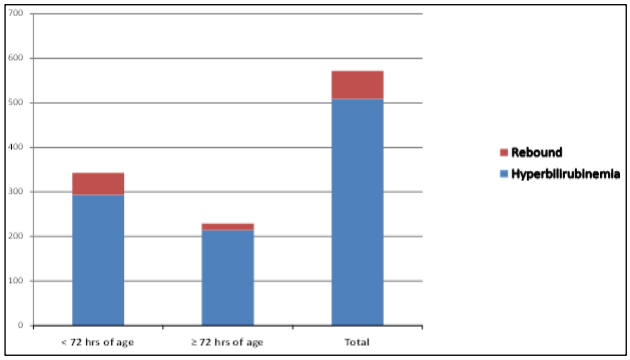

Figure 3: Age of onset of hyperbilirubinemia and rebound.

DISCUSSION

Incidence of significant bilirubin rebound after stopping phototherapy for 24±6 hours in the present study was found to be 12% which is well in tune with the published studies in literature which have reported it in 5.1 to 13.2% of cases.[8,9,11] Wide variations in the incidence could be due to the study plans not being uniform with regard to timing of measurement of bilirubin post phototherapy, prematurity, birth weight and presence of other risk factors like blood group incompatibility, G6PD deficiency and others.[11]

At highest risk for SBR are premature infants or those with a positive direct Coombs test, severity and onset of hyperbilirubinemia, mode of feeding and presence of other risk factors like G6PD deficiency.[5,9,11] In the present study SBR in neonates was analyzed according to etiological subgroups and we found that factors

influencing SBR were prematurity, ABO and Rh incompatibility between mother and baby and G6PD deficiency and onset of hyperbilirubinemia <72 hours of age.

Incidence of prematurity (21%) in the present study was comparable with that of Bansal et al (22.5%) and Kaplan et al (21.9%). Prematurity as a cause of SBR in comparison to term babies was statistically significant ($p<0.01$) and agrees with other studies.[9,11]

ABO and Rh incompatibility together accounted for 21% of cases of hyperbilirubinemia and around 1/4th of these developed rebound of magnitude requiring reinstitution of phototherapy and was statistically significant (P <0.001 and <0.005 respectively). Kaplan et al have reported 56% incidence of coombs positive ABO incompatibility and 14.5% of these developed statistically significant rebound (odds ratio 2.44, 95% CI 1.25 to 4.74, p=0.028).[11] Comparatively higher incidence in present study may be due to coombs positive and negative hemolytic anemias being grouped together.

Postnatal age of onset of hyperbilirubinemia influences the rate of rebound as observed by Kaplan et al,17% of neonates rebounded among those in whom phototherapy was commenced (<72 hours) compared to 5.4% in >72 hours (odds ratio 3.61, 95% CI 1.21 to10.77). Rate of rebound in the present study in both the groups <72 hours and >72 hours, 16.7% versus 6.5% (P < 0.001, OR 2.87 CI 1.54-5.35**)** was comparable with the above study.

There are conflicting reports in literature regarding recommendations for estimation of post phototherapy bilirubin, some of them are of the opinion that delay in hospital discharge and follow up of rebound is not required regardless of the background attributes of newborns since SBR is rare.[3-5,7,8,13] AAP 2004 guidelines recommend a follow up bilirubin measurement after 24 hours of discharge, though discharge from hospital need not be delayed for the same.[10]

However, our observations are in tune with Saad A et al, Erdeve O et al, Bansal et al, Kaplan et al and most recently B Jodeiry et al who recommend that a rebound bilirubin level must be obtained in high-risk neonates.[7-9,11,12] In addition Bansal et al also proposed delay in discharge for this purpose if follow-up cannot be ensured as is felt during current study. The decision not to estimate rebound bilirubin levels should be carefully balanced as phototherapy has no long term adverse effects as very well established by Stanley I et al in their study of multiple case reports.[13].

CONCLUSION

In light of study data, we recommend that neonates < 37 weeks gestation, those with ABO and Rh incompatibility, G6PD deficiency and those who developed hyperbilirubinemia requiring phototherapy less than 72 hours of age, are at high risk for significant post-phototherapy rebound. Delay in discharge is a good option for this purpose in high-risk situations where follow-up cannot be guaranteed particularly in places like ours where patients are from far flung difficult and tribal areas.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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