Original Article

Clinical study to determine the predictability of significant rebound hyperbilirubinemia in neonates after phototherapy and conditions likely to be associated with it: Prospective observational study in a teaching hospital in Eastern India

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Abstract

Aim: Neonatal hyperbilirubinemia is defined as yellowish discoloration of the skin, conjunctive, and sclera from the elevated serum or plasma bilirubin in the newborn. The standard of care for the management of neonatal hyperbilirubinemia is phototherapy to prevent long-term neurological sequelae. The aim of this study was to ascertain the predictability of significant rebound hyperbilirubinemia (SRH) in neonates after phototherapy and the factors associated with it. **Materials and Methods:** Neonates ≥ 35 weeks of gestation, who received treatment for hyperbilirubinemia and admitted in our hospital from 15th of March 2019 to 15th of September 2020 were enrolled after taking parental consent. SRH was defined as bilirubin levels crossing the treatment threshold within 72 hours of phototherapy termination. Logistic regression analysis was used to identify the predictability of SRH. **Results:** Out of 400 neonates treated with phototherapy, 10% developed SRH. Prematurity (Gestational age < 37 weeks), low birth weight (Birth weight < 2000 gram), ABO and Rh incompatibility, Glucose-6-phophate dehydrogenase deficiency (G6PD) deficiency, sepsis, and longer duration of primary phototherapy were found to be significantly associated with rebound hyperbilirubinemia. The probability of SRH increases for all American Academy of Paediatrics (AAP) risk categories as the gestational age decreases and total serum bilirubin at the stoppage of phototherapy increases. **Conclusions:** The presence of risk factors should be taken into account while planning discharge and follow-up of neonates admitted for neonatal hyperbilirubinemia to prevent long-term complication of bilirubin neurotoxicity.

Keywords: Hyperbilirubinemia, phototherapy, predictability, rebound hyperbilirubinemia

Introduction

Neonatal hyperbilirubinemia is defined as yellowish discoloration of the skin, conjunctive, and sclera from the elevated serum or plasma bilirubin in the newborn. The standard of care for the management of neonatal hyperbilirubinemia is phototherapy to prevent long-term neurological dysfunction. Neonatal hyperbilirubinemia is the most common morbidity affecting nearly half of the term and 80% of preterm babies in the early neonatal period and one of the common causes of readmission.[1,2] Treatment and close follow-up of high-risk babies for neonatal hyperbilirubinemia is a matter of considerable debate because of bilirubin-induced neurological dysfunction and its sequelae.[3]

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Scarcity of resources, loss to follow-up, ignorance regarding neurodevelopment sequelae, and emotional trauma to the mother due to repeated pricks to the baby for blood sampling are a few reasons for the high incidence of SRH in developing countries. The aim of this study was to ascertain the predictability of significant rebound hyperbilirubinemia (SRH) in neonates after phototherapy and the factors associated with it.

Materials and Methods

This was a prospective observational study done in the neonatal unit of a teaching institute in eastern India for a period of 18 months from 15th of March 2019 to 15th of September 2020. All the neonates were included at the gestational age ≥ 35 weeks with neonatal hyperbilirubinemia requiring phototherapy as per American Academy of Paediatrics (AAP) guideline,[4] whose parents have given the informed consent for the study. Neonates with < 35 weeks of gestation and seriously ill babies and babies with major congenital malformations were excluded. As per our unit protocol, to identify the underlying etiology, on admission investigations like total serum bilirubin (TSB), complete blood count with peripheral smear, blood grouping, reticulocyte count, Glucose-6-phosphate dehydrogenase (G6PD), direct comb test (DCT), thyroid stimulating hormone (TSH), and additional investigations like urine routine, microscopy and culture sensitivity, blood culture sensitivity, and osmatic fragility test were done as and when clinically indicated.

Phototherapy was administered by a light emitting diode (LED) blue light (Lullaby GE) with an irradiance of 30 μW/cm^2/nm. TSB was monitored between 6 and 12 hours in neonates requiring phototherapy for hyperbilirubinemia and every 4–6 hours in babies with serum bilirubin levels approaching the exchange transfusion threshold. Phototherapy was turned off once TSB dropped to 2 mg/dl below the treatment threshold as per AAP guidelines. After discontinuation of phototherapy, TSB was checked after 24 hours for rebound hyperbilirubinemia (as per our unit protocol). If the TSB after 24 hours of stoppage of phototherapy increase to the age and gestation specific cut-off as per AAP guidelines and charts, phototherapy was reinstituted, and second course of phototherapy was continued till TSB level decreases to less than 3 mg/dl for age and gestation specific cut-off as per our unit protocol. SRH is defined as an increase in the TSB to a level requiring a second course of phototherapy. A pre-tested proforma with standard definitions was used to register the cases after obtaining institutional ethical committee approval.

Data management and data analysis

The sample size in the present study was 400, calculated by using *Epiinfo 6* for population survey, which requires population size, the expected frequency, the worst acceptable frequency, and the confidence level of the study. Collected data was stored and tabulated in the master chart in the MS Excel version 10 spreadsheets. Discrete data is expressed in the outline of frequencies and percentages. Continuous data is expressed in terms of "Mean ± Standard Deviation." "Chi-Square Test" is used to analyze the categorical data and "Student t-test" is used to analyze the continuous data. Predictive analysis was done by using "Logistic Regression Equations." Statistical significance is set at the level of 0.05 for the practical purposes. SPSS version 16 was used for the statistical analysis and predictive analysis.

Results

A total of 400 neonates were included. Of these, 40 (10%) developed SRH [Table 1].

The "SRH" was statistically significant in those babies who were preterm, with birth weight < 2000-gram, ABO and Rh incompatible, G6PD deficient, and babies with sepsis. As per the AAP risk categories, "SRH" was maximum in patients with high-risk (24.24%) as compared to the low-risk (6.82%) and medium-risk (7.32%) and the difference between them was statistically significant (*P* value < 0.05) [Table 2].

The duration of primary phototherapy in babies with "SRH" was more than "non-SRH" babies (Mean {SD} 35.48 {7.61} hours: 18.2 {9.10} hours), and it was statistically significant. In patients with SRH, the mean duration of re-phototherapy was found to be 29.18 hours with a standard deviation of ± 4.30 hours [Table 3].

Predictability

The predictability of SRH after 24 hours of stoppage of phototherapy was decided based on gestational age and TSB at the stoppage of phototherapy using the regression analysis equation. The patients were divided into three categories as per AAP risk categories[4] and the pattern of predictability based on gestational age and TSB at stoppage of phototherapy for these risk categories. The regression analysis was used for making the equations using gestational age and TSB at a stoppage of phototherapy as independent variables and TSB at 24 hours after the stoppage of phototherapy as dependent variables ($y = a + bx$, where y is dependent variable, x is independent variable and a and b are constants).

From the regression analysis [Figures 1-3], it could be seen that the slope of the graph was negative, that is, the value of TSB at 24 hours after stoppage of phototherapy (rebound hyperbilirubinemia, dependent variable, y) and their value was increasing negatively with increasing risk. Thus, we could predict that as the gestational age increases, the risk of rebound hyperbilirubinemia decreases. The lower gestational-aged neonates had a higher risk of rebound hyperbilirubinemia.

From the regression analysis [Figures 4-6], it could be seen that the slope of the graph is positive, that is, the value of

Table 1: Incidence of SRH

Condition	No of Cases	Percentage
With SRH	40	10%
No "SRH"	360	90%

Table 2: Risk factors for SRH

Parameter	Total	With Significant Rebound Hyperbilirubinemia	Without Significant Rebound Hyperbilirubinemia	*P*
Gender-wise				
Male	204 (51%)	24 (11.76%)	180 (88.24%)	0.230
Female	196 (49%)	16 (8.16%)	180 (91.84%)	
Mode of delivery				
NVD	286 (71.5%)	30 (10.49%)	256 (89.51%)	0.605
LSCS	114 (28.5%)	10 (8.77%)	104 (91.23%)	
Gestational age				
Preterm (<37 weeks)	240 (60%)	31 (12.92%)	209 (87.08%)	0.017
Term (≥37 weeks)	160 (40%)	9 (5.63%)	151 (94.37%)	
Birth weight				
<2000 gm	32 (8%)	7 (21.87%)	25 (78.13%)	0.020
≥2000 gm	368 (92%)	33 (8.97%)	335 (91.03%)	
Mode of feeding				
Breast Feeding	323 (80.75%)	32 (9.91%)	291 (90.09%)	0.980
Formula Feed	66 (16.5%)	7 (10.61%)	59 (89.39%)	
IV Fluids	11 (2.75%)	1 (9.09%)	10 (90.91%)	
AAP risk category				
Low-Risk	88 (22%)	6 (6.82%)	82 (93.18%)	0.0001
Medium-Risk	246 (61.5%)	18 (7.32%)	228 (92.68%)	
High-Risk	66 (16.5%)	16 (24.24%)	50 (75.76%)	
ABO/Rh Incompatibility	77 (19.25%)	16 (20.78%)	61 (79.22%)	0.0004
Without ABO/Rh Incompatibility	323 (80.75%)	24 (7.43%)	299 (92.57%)	
Sepsis +	37 (9.25%)	11 (29.73%)	26 (70.7%)	0.000
Sepsis -	363 (90.75%)	29 (7.99%)	334 (92.01%)	
G6PD deficiency +	12 (3%)	4 (33.33%)	8 (66.67%)	0.006
G6PD deficiency –	388 (97%)	36 (9.28%)	352 (90.72%)	

Table 3: Mean duration of primary phototherapy and re-phototherapy

Duration of phototherapy	Mean	Standard deviation	*P*
Duration of primary phototherapy in "Non-SRH" neonates (in hrs)	18.2	±9.10	0.000
Duration of primary phototherapy in "SRH" neonates (in hrs)	35.48	±7.1	
Re-Phototherapy duration in "SRH" neonates (in hours)	29.18	±4.30	

TSB at 24 hours after stoppage of phototherapy (rebound hyperbilirubinemia, dependent variable, y) increases with an increase in the value of TSB at stoppage of phototherapy (primary phototherapy) (independent variable, x). Thus, we could predict that as the TSB at a stoppage of phototherapy increases, the risk of rebound hyperbilirubinemia increases. Thus, higher TSB at stoppage of phototherapy, higher risk of rebound hyperbilirubinemia.

Discussion

On extensive review of the literature, we found there are few studies on predictability for rebound hyperbilirubinemia. In this study, we have reported the incidence and risk factors for SRH after discontinuation of intensive phototherapy and the predictability of "SRH" for gestational age and the value of

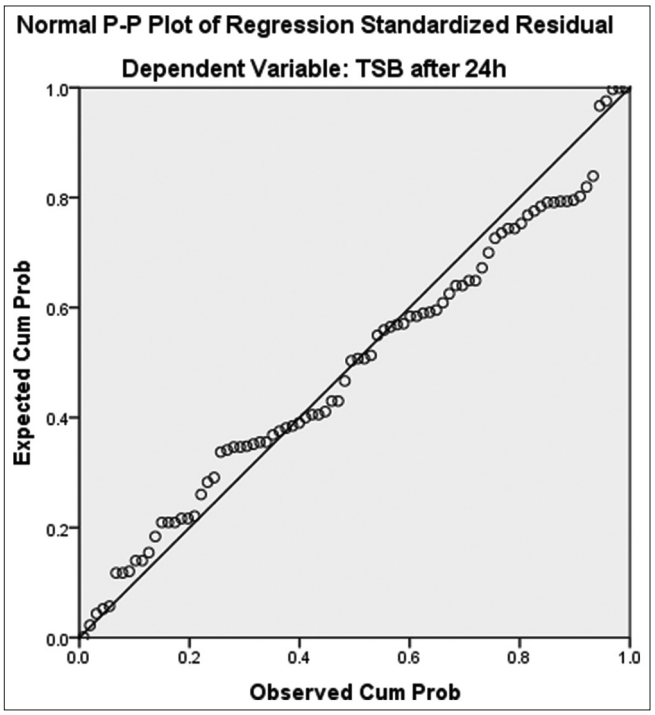

Figure 1: Predictability in relation to gestational age with AAP low-risk category

TSB at stoppage of phototherapy for all AAP risk categories. This is the first of its kind of study as per our best knowledge

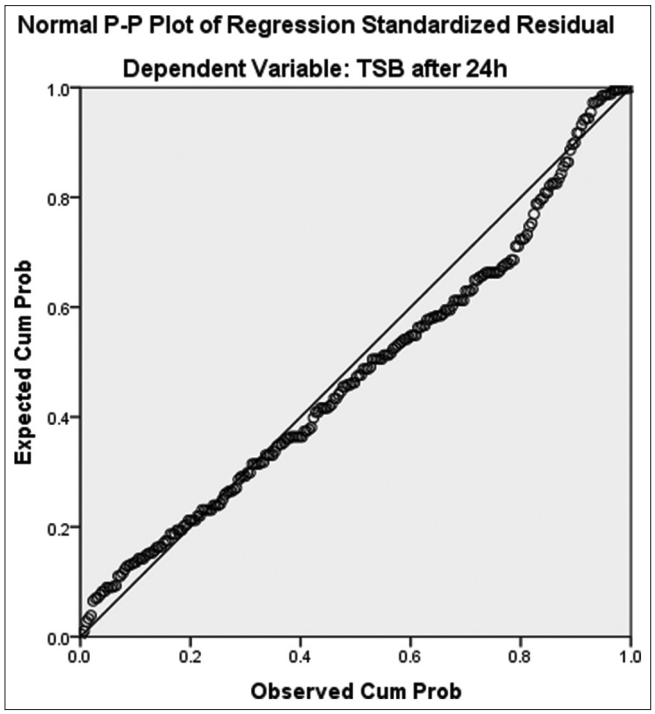

Figure 2: Predictability in relation to gestational age with AAP medium-risk category

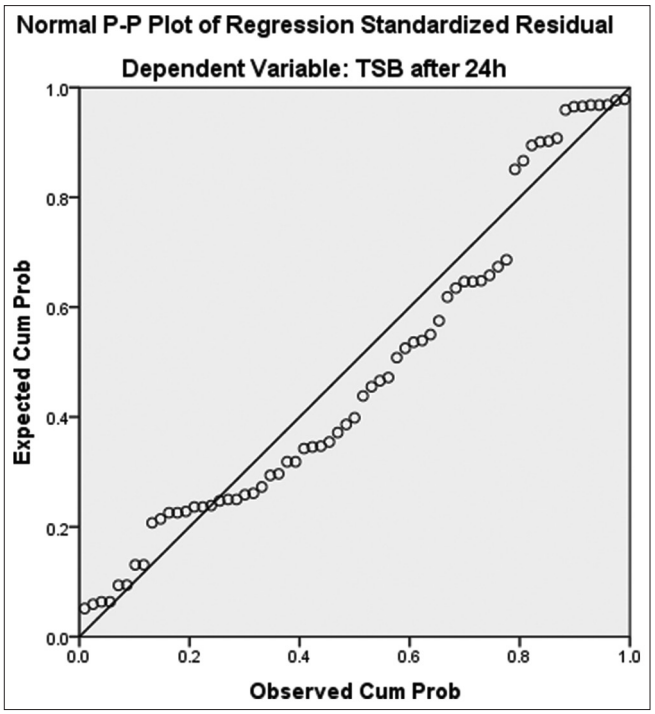

Figure 3: Predictability in relation to gestational age with AAP high-risk category

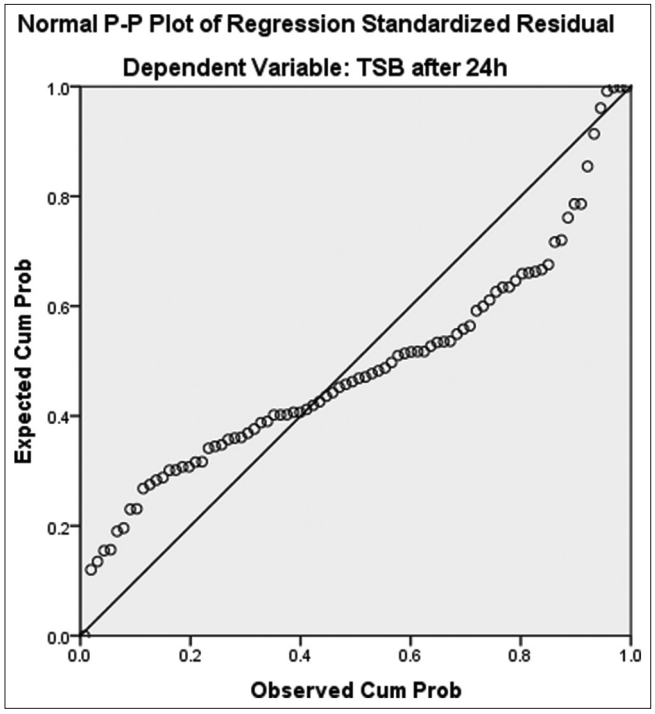

Figure 4: Predictability in relation to TSB at stoppage of phototherapy with AAP low-risk category

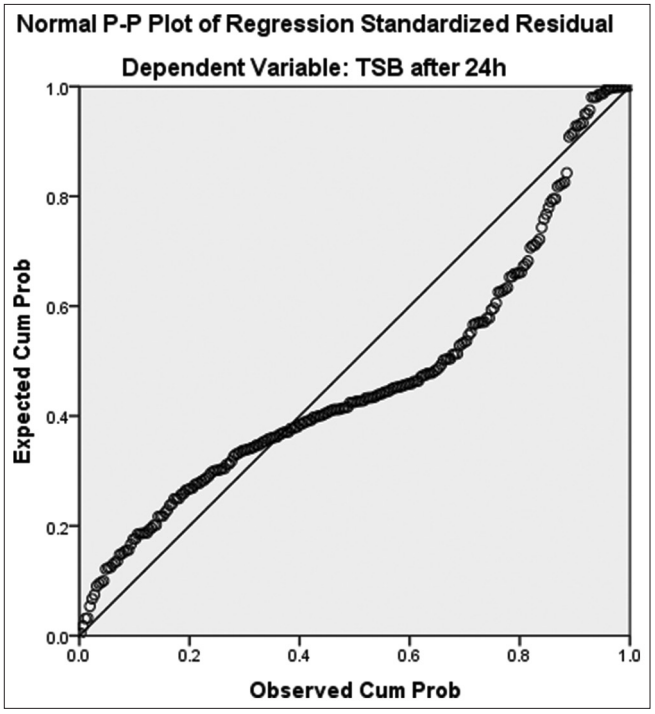

Figure 5: Predictability in relation to TSB at stoppage of phototherapy with AAP medium-risk category

from India about the incidence, risk factors, and predictability of "SRH."

The present study involved 400 neonates (240 terms and 160 preterm) both inborn and outborn with neonatal jaundice who received phototherapy during the study period. They were subsequently examined for rebound hyperbilirubinemia usually 24 hrs after stoppage of phototherapy. Out of total 400 neonates, 40 (10%) neonates developed SRH following 24 hours after the termination of phototherapy. This finding

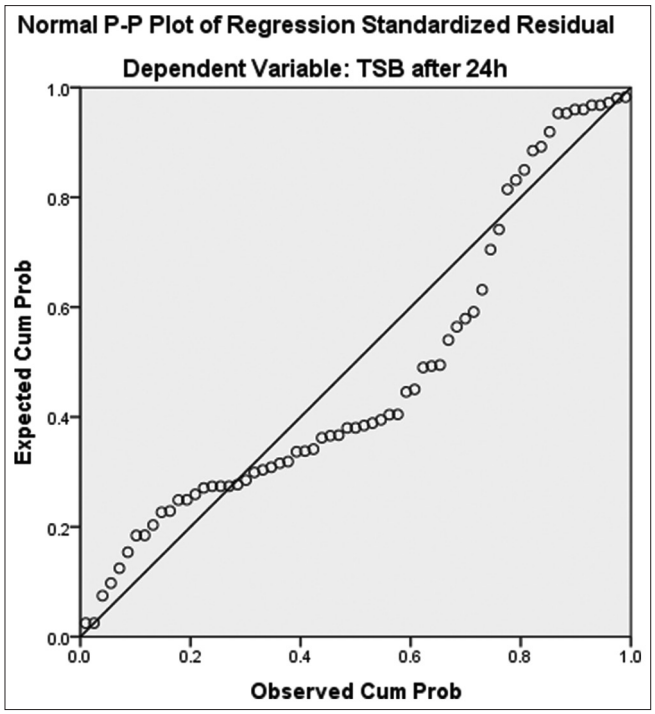

Figure 6: Predictability in relation to TSB at stoppage of phototherapy with AAP high-risk category

is comparable with other studies which had reported it in 5.1–13.2% of cases.[5-7]

In the present study, "SRH" in neonates was analyzed and the factors influencing "SRH" were prematurity (<37 weeks gestation), low birth weight (<2000 gram), ABO and Rh incompatibility, G6PD deficiency and sepsis and these were statistically significant (*P* value < 0.05) and these observations were similar to the other studies.[5,7,8] In our study, higher primary phototherapy duration in "SRH" neonates (Mean 35.48 ± 7.61 hrs) than in non-SRH neonates (Mean 18.2 ± 9.1 hrs) with statistical significance (*P* value < 0.05) indicates that the chance of bilirubin rebound was more in those babies required more time to normalize the initial bilirubin level.

Using the regression analysis equation, we observed that as the gestational age increases, the risk of rebound hyperbilirubinemia decreases and as serum bilirubin at stoppage of phototherapy increases, the risk of rebound hyperbilirubinemia in all AAP risk categories increases. These observations were similar to the studies conducted by Chang *et al.*[9,10]

All 40 babies with SRH were treated with only intensive phototherapy for a variable duration (mean 20.53 ± 5.58 hrs) without other forms of therapy like exchange transfusion and intravenous immunoglobulin (IV Ig), all babies recovered uneventfully suggesting that retreatment with intensive phototherapy was found to be an effective therapy for babies with "SRH."

Our observations were supported with the studies done by Kaplan *et al.*, Erdeve *et al.*, Bansal *et al.*, and Al-Saedi; all studies recommend that a rebound TSB level must be measured in high-risk newborn babies.[5-7,11] Delay in the discharge of high-risk babies should be advised if follow-up could not be ensured.[7]

Limitations of our study

Our study has limitation that it was a hospital-based study and with gestation of 35 weeks and above was taken into account, it is not attainable to deduce the results to level of whole community as many factors impact the development of SRH.

Conclusion

The presence of risk factors should be taken into account while planning discharge and follow-up of neonates admitted for neonatal hyperbilirubinemia to prevent long-term complication of bilirubin neurotoxicity. Measurement of serum bilirubin level after stopping of phototherapy is recommended especially in the presence of risk factors like prematurity, ABO and Rh incompatibility, G6PD deficiency, birth weight < 2000 grams, sepsis, and prolonged primary phototherapy duration. Gestational age and TSB at a stoppage of phototherapy help in predicting SRH.

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Conflicts of interest

There are no conflicts of interest.

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