e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(8); 950-955

Original Research Article

Risk Factors Associated with Significant Rebound Hyperbilirubinemia Following Phototherapy in Neonates: An Observational Study

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Received: 04-07-2026 / Revised: 15-07-2026 / Accepted: 25-07-2026
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Conflict of interest: Nil

Abstract

Objective: To evaluate the risk factors associated with rebound hyperbilirubinemia after phototherapy in neonates admitted to Government Medical College and Hospital, Jaisalmer.

Methodology: The study included all neonates with a gestational age of ≥35 weeks admitted to the Neonatal Intensive Care Unit and postnatal wards of Government Medical College and Hospital, Jaisalmer, who required phototherapy for unconjugated hyperbilirubinemia. Phototherapy was initiated and discontinued according to standard treatment guidelines. Rebound serum bilirubin was measured 24 ± 6 hours after cessation of phototherapy. Significant rebound hyperbilirubinemia (SBR) was defined as a post-phototherapy bilirubin level requiring reinstitution of phototherapy. Maternal, neonatal, and treatment-related risk factors associated with SBR were evaluated.

Results: Of the 153 neonates included, 21 (13.7%) developed significant rebound hyperbilirubinemia (SBR). Gestational age <38 weeks, birth weight <2500 g, ABO incompatibility, Rh incompatibility, initiation of phototherapy within 72 hours of life, and higher total serum bilirubin at discontinuation of phototherapy were significantly associated with SBR ($p<0.05$). G6PD deficiency was more frequent among neonates with SBR but did not reach statistical significance because of the small number of affected infants. Neonates with SBR also had significantly higher rebound bilirubin levels 24 ± 6 h after discontinuation of phototherapy ($p<0.001$).

Conclusion: Assessment of clinical and treatment-related risk factors should guide decisions regarding post-phototherapy monitoring and discharge. A risk-based follow-up strategy may aid in the timely identification of rebound hyperbilirubinemia and minimize the risk of bilirubin neurotoxicity.

Keywords: Neonatal Hyperbilirubinemia, Rebound Hyperbilirubinemia, Phototherapy, Risk Factors.

DOI: 10.25258/ijcpr.18.7.145

Introduction

Neonatal hyperbilirubinemia is one of the most common clinical conditions encountered during the neonatal period, affecting approximately 60% of term and 80% of preterm neonates during the first week of life. Although most cases are physiological and self-limiting, severe hyperbilirubinemia may result in acute bilirubin encephalopathy and kernicterus if not recognized and treated promptly.[1,2] Phototherapy is the standard treatment for unconjugated neonatal hyperbilirubinemia and has markedly reduced the need for exchange transfusion.

Current recommendations advocate initiation and discontinuation of phototherapy according to standardized treatment thresholds to achieve effective bilirubin reduction while minimizing unnecessary hospitalization.[1,3] Following discontinuation of phototherapy, serum bilirubin levels may rise again because the underlying mechanism responsible for hyperbilirubinemia may persist. While this rebound is usually mild, a proportion of neonates develop significant rebound hyperbilirubinemia requiring reinstitution of phototherapy.[4,5] The reported incidence of significant rebound hyperbilirubinemia varies across studies depending on the study population, gestational age, etiology of jaundice, and criteria used to define rebound.

Previous studies have identified prematurity, low birth weight, hemolytic disease, early initiation of phototherapy, higher bilirubin levels at discontinuation, and prolonged phototherapy as important risk factors.[4-8] However, routine post-phototherapy bilirubin estimation for all neonates remains controversial because universal testing may prolong hospital stay and increase healthcare

costs. Identification of neonates at high risk of rebound hyperbilirubinemia would allow selective monitoring, timely intervention, and safe discharge planning. [4,6-8]

Indian data on significant rebound hyperbilirubinemia remain limited, with variations in the reported incidence and associated risk factors among different regions of the country. [4,5] Therefore, the present study was undertaken to determine the incidence of significant rebound hyperbilirubinemia after phototherapy and to identify the maternal, neonatal, and treatment-related factors associated with its occurrence in neonates admitted to Government Medical College and Hospital, Jaisalmer.

Method

This prospective observational cohort study was conducted in the Neonatal Intensive Care Unit and postnatal wards of Government Medical College and Hospital, Jaisalmer for the period of 3 months. Consecutive neonates with gestational age ≥ 35 weeks requiring phototherapy for unconjugated hyperbilirubinemia were enrolled.

Phototherapy was initiated and discontinued according to standard treatment guidelines. Total serum bilirubin was measured 24 ± 6 hours after discontinuation of phototherapy. Significant rebound hyperbilirubinemia was defined as a post-phototherapy bilirubin level requiring reinstitution of phototherapy. Maternal, neonatal, and treatment-related risk factors associated with significant rebound hyperbilirubinemia were analyzed using appropriate statistical methods. The study was approved by the Institutional Ethics and research Committee. Written informed consent was obtained from parents/guardians.

Inclusion Criteria:

- Neonates with gestational age ≥35 weeks.
- Neonates with unconjugated hyperbilirubinemia requiring phototherapy according to standard treatment guidelines.
- Neonates admitted to the Neonatal Intensive Care Unit (NICU) or postnatal wards of Government Medical College and Hospital, Jaisalmer.
- The newborns, whose parents / guardians give informed consent.

Exclusion Criteria:

- Neonates with conjugated hyperbilirubinemia.
- Neonates who underwent exchange transfusion before completion of phototherapy.
- Neonates with major congenital anomalies or chromosomal disorders.
- Critically ill neonates requiring invasive respiratory support or having severe systemic illness (e.g., septic shock).
- Neonates with birth asphyxia or hypoxic-ischemic encephalopathy

Sample Size and Sampling Method: The sample size was calculated using an expected prevalence of significant rebound hyperbilirubinemia of 10% based on a previous prospective Indian study. At a 95% confidence level and 5% absolute precision, the minimum required sample size was 139. After allowing for a 10% attrition rate, the final sample size was 153 neonates. Consecutive sampling was used. All eligible neonates meeting the inclusion criteria and requiring phototherapy during the study period were enrolled until the required sample size was achieved.

Methodology

The newborns were selected as per inclusion and exclusion criteria. Demographic, maternal, clinical, and laboratory data were collected using a predesigned case record proforma. Variables recorded included gestational age, birth weight, sex, mode of delivery, maternal age, feeding pattern, ABO/Rh blood group incompatibility, etiology of jaundice, age at initiation and duration of phototherapy, and total serum bilirubin levels at initiation, discontinuation, and 24 ± 6 hours after cessation of phototherapy. Phototherapy was initiated and discontinued according to standard institutional guidelines. Significant rebound hyperbilirubinemia (SBR) was defined as a post-phototherapy serum bilirubin level requiring reinstitution of phototherapy as per standard treatment guidelines. The incidence of SBR and its association with potential clinical risk factors were evaluated.

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation and categorical variables as frequencies and percentages. Comparisons were performed using the Student's t-test, Chi-square test or Fisher's exact test, as appropriate. A p-value <0.05 was considered statistically significant.

Results

A total of 153 neonates who received phototherapy for unconjugated hyperbilirubinemia were included in the study. Of these, 21 (13.7%) developed significant rebound hyperbilirubinemia (SBR), while 132 (86.3%) did not. The baseline demographic and clinical characteristics of the study population are presented in Table 1.

The comparison of demographic, clinical, and laboratory characteristics between neonates with and without SBR is shown in Table 2. Neonates with gestational age <38 weeks had a significantly higher incidence of SBR than those born at ≥38

weeks (52.4% vs 23.5%, p=0.008). Similarly, birth weight <2500 g was significantly associated with SBR (42.9% vs 22.7%, p=0.041).

Among the etiological factors, ABO incompatibility (42.9% vs 14.4%, p=0.002) and Rh incompatibility (19.0% vs 5.3%, p=0.026) were significantly more common in neonates who developed SBR. Although G6PD deficiency was more frequent among neonates with SBR (4.8% vs 1.5%), the association was not statistically significant (p=0.44).

No significant association was observed with male sex (p=0.96), cesarean delivery (p=0.53), sepsis (p=0.39), cephalhematoma/ bruising (p=0.22), idiopathic jaundice (p=0.39), polycythemia (p=0.96), delayed passage of meconium (p=0.44), or exclusive breastfeeding (p=0.97). Phototherapy initiated within the first 72 hours of life was significantly associated with SBR (71.4% vs 40.2%, p=0.007), whereas duration of phototherapy >48 hours was not significantly associated with rebound hyperbilirubinemia (p=0.18).

The mean total serum bilirubin level at discontinuation of phototherapy was significantly higher among neonates with SBR than those without SBR (12.5 ± 1.1 mg/dL vs 11.6 ± 1.2 mg/dL, p=0.003). Likewise, the mean rebound bilirubin level measured 24 ± 6 hours after discontinuation of phototherapy was significantly higher in the SBR group (15.4 ± 1.6 mg/dL vs 11.2 ± 1.3 mg/dL, p<0.001).

Table 1: Baseline characteristics, etiology and risk factors among neonates with unconjugated hyperbilirubinemia (n = 153)

Variable	Number of neonates	n (%)
Gestational age <38 weeks	42	27.5
Birth weight <2500 g	39	25.5
Male sex	88	57.5
Cesarean delivery	63	41.2
ABO incompatibility	28	18.3
Rh incompatibility	11	7.2
G6PD deficiency	3	2.0
Sepsis	15	9.8
Cephalhematoma/bruising	18	11.8
Polycythemia	7	4.6
Delayed passage of meconium	10	6.5
Exclusive breastfeeding	117	76.5
Phototherapy started <72 h of life	68	44.4
Phototherapy duration >48 h	34	22.2
Idiopathic jaundice	41	26.8

Table 2: Comparison of clinical and laboratory characteristics between neonates with and without significant rebound hyperbilirubinemia

Variable	No SBR (n = 132)	SBR (n = 21)	P value
Gestational age <38 weeks, n (%)	31 (23.5)	11 (52.4)	0.008
Birth weight <2500 g, n (%)	30 (22.7)	9 (42.9)	0.041
Male sex, n (%)	76 (57.6)	12 (57.1)	0.96
Cesarean delivery, n (%)	53 (40.2)	10 (47.6)	0.53
ABO incompatibility, n (%)	19 (14.4)	9 (42.9)	0.002
Rh incompatibility, n (%)	7 (5.3)	4 (19.0)	0.026
G6PD deficiency, n (%)	2 (1.5)	1 (4.8)	0.44
Sepsis, n (%)	12 (9.1)	3 (14.3)	0.39
Cephalhematoma/bruising, n (%)	14 (10.6)	4 (19.0)	0.22
Polycythemia, n (%)	6 (4.5)	1 (4.8)	0.96
Delayed passage of meconium, n (%)	8 (6.1)	2 (9.5)	0.44
Exclusive breastfeeding, n (%)	101 (76.5)	16 (76.2)	0.97
Phototherapy initiated <72 h of life, n (%)	53 (40.2)	15 (71.4)	0.007
Duration of phototherapy >48 h, n (%)	27 (20.5)	7 (33.3)	0.18
Mean bilirubin at discontinuation of phototherapy (mg/dL), Mean ± SD	11.6 ± 1.2	12.5 ± 1.1	0.003
Mean rebound bilirubin after 24 ± 6 h (mg/dL), Mean ± SD	11.2 ± 1.3	15.4 ± 1.6	<0.001
Idiopathic jaundice	37 (28.0%)	4 (19.0%)	0.39

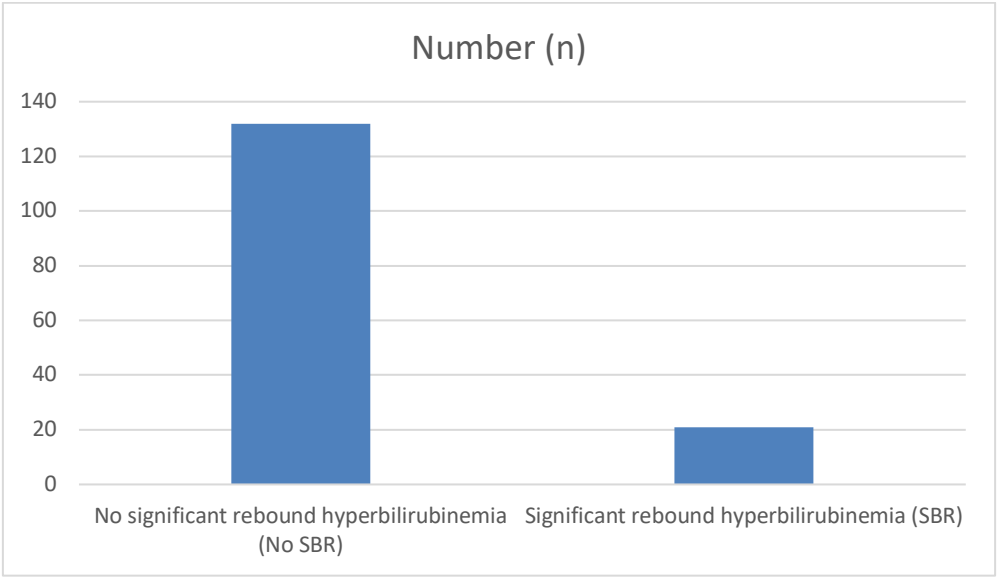

Figure 1: Incidence of significant rebound hyperbilirubinemia following phototherapy.

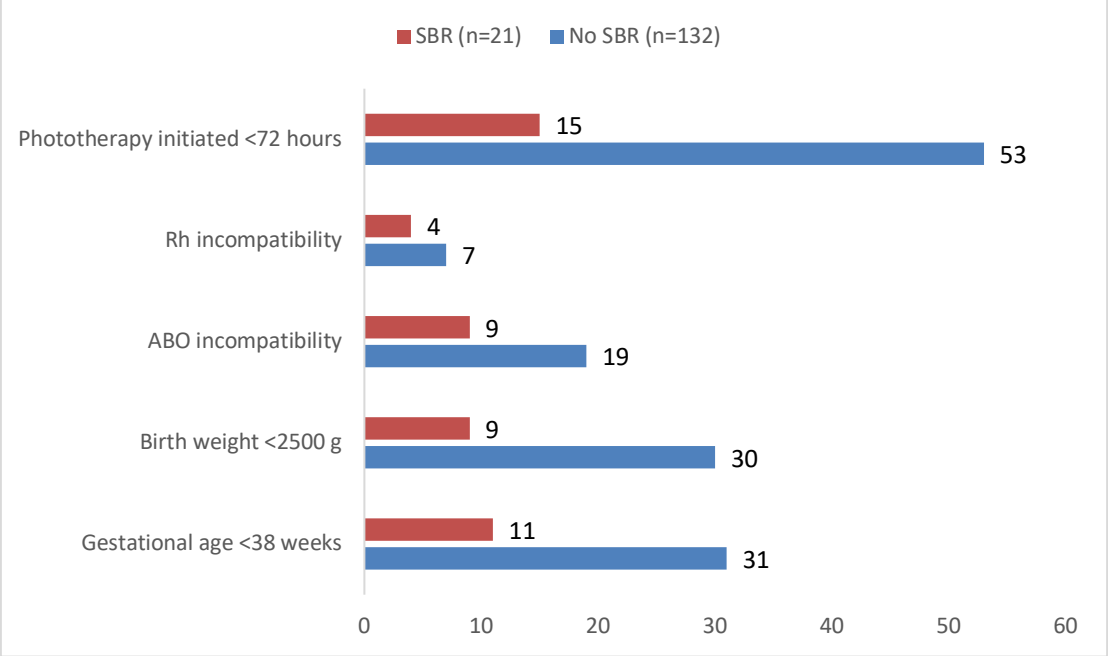

Figure 2: Distribution of statistically significant risk factors associated with significant rebound hyperbilirubinemia

Discussion

In the present study, the incidence of significant rebound hyperbilirubinemia (SBR) following discontinuation of phototherapy was 13.7%. This incidence is comparable to previous reports, which have documented rates ranging from approximately 4% to 13% depending on the study population, timing of rebound bilirubin estimation, and criteria used to define rebound hyperbilirubinemia.

Earlier studies by Kaplan et. al. [3] and Bansal et. al. [2] reported incidences of 8.2% and 12%, respectively, while Elhawary et. al. [7] and Belide et. al. [5] observed comparable rates in high-risk neonates. More recently, Kamaladevi BC et al. [8] reported a lower incidence of 5.6% among late preterm and term infants, reflecting differences in patient selection and exclusion of high-risk neonates. Earlier studies by Yetman et al. [9] demonstrated that bilirubin rebound after phototherapy is generally minimal in most healthy term infants and suggested that routine post-phototherapy bilirubin measurement may not be necessary. Del Vecchio et al. [10] further emphasized that clinically significant rebound is uncommon in the absence of recognized risk factors. Maisels and Kring [11] reported that although a modest rise in serum bilirubin

commonly occurs after discontinuation of phototherapy, only a small proportion of infants require reinstitution of treatment. Similarly, Al-Saeedi [12] observed a low incidence of clinically significant rebound hyperbilirubinemia among term neonates and questioned the value of routine rebound bilirubin estimation in all infants. Erde et al. [13] also concluded that routine post-phototherapy bilirubin measurement is unnecessary for most newborns and recommended selective monitoring based on individual clinical risk factors. Together, these studies laid the foundation for the current practice of risk-based rather than universal rebound bilirubin monitoring.

Gestational age below 38 weeks was significantly associated with SBR in our study. Prematurity has consistently been recognized as an important risk factor because of hepatic immaturity, increased enterohepatic circulation, and reduced bilirubin conjugation. Similar findings were reported by Kaplan et. al. [3], Bansal et. al. [2], Chang et. al. [6], and Elhawary et. al. [7], all of whom identified lower gestational age as an important determinant of rebound hyperbilirubinemia.

Low birth weight (<2500 g) was also significantly associated with rebound hyperbilirubinemia. Low birth weight often reflects physiological immaturity and may coexist with prematurity, resulting in prolonged bilirubin metabolism and an increased likelihood of rebound after discontinuation of phototherapy. Comparable findings have been reported by Bansal et. al. [2] and Belide et. al. [5], while the recent prediction model developed by Kamaladevi BC et al. [8] also incorporated birth weight among the variables used for estimating rebound risk.

Among the etiological factors, ABO incompatibility and Rh incompatibility showed significant associations with SBR. Ongoing hemolysis continues bilirubin production even after phototherapy has been discontinued, predisposing these neonates to rebound hyperbilirubinemia. Similar findings have been reported by Bansal et al. [2], Kaplan et al. [3], Belide et al. [5], Chang et al. [6], and Elhawary et al. [7], confirming hemolytic conditions as important risk factors for rebound hyperbilirubinemia. Kaplan et al. [3] were the first to emphasize the increased risk among infants with hemolytic disease. Although G6PD deficiency was more common among neonates with SBR in the present study, the association did not reach statistical significance, probably because of the very small number of affected neonates (3 cases) included in the analysis.

In contrast, male sex, mode of delivery, sepsis, cephalhematoma or bruising, idiopathic jaundice, polycythemia, delayed passage of meconium, and exclusive breastfeeding were not significantly associated with rebound hyperbilirubinemia in the present study. Similar observations have been reported by Bansal et. al. [2], Soni et. al. [4], Belide et. al. [5], and Elhawary et. al. [7], suggesting that although these conditions may contribute to neonatal jaundice, they are less reliable indicators of clinically significant rebound after phototherapy.

Phototherapy initiated within the first 72 hours of life was significantly associated with SBR in our study. Early-onset jaundice is frequently related to hemolysis or other pathological causes and therefore carries a greater risk of bilirubin rebound. Similar observations have been described by Bansal et. al. [2], Elhawary et. al. [7], and Belide et. al. [5], who also reported that earlier onset of hyperbilirubinemia was associated with an increased likelihood of rebound requiring repeat phototherapy. However, duration of phototherapy exceeding 48 hours did not show a statistically significant association with SBR, suggesting that the underlying etiology rather than treatment duration may be the principal determinant of rebound.

Neonates who developed SBR had significantly higher mean total serum bilirubin levels at discontinuation of phototherapy and markedly higher rebound bilirubin concentrations after phototherapy. Chang et. al. [6] developed a clinical prediction model demonstrating that bilirubin levels relative to the treatment threshold at discontinuation, together with gestational age, accurately predict rebound risk. This model was subsequently validated in an independent cohort by Chandrasekar Kamaladevi et. al. [8], supporting individualized risk assessment rather than universal rebound bilirubin estimation.

The findings of the present study support the current American Academy of Pediatrics (AAP) 2022 guideline [1], which recommends selective post-phototherapy bilirubin measurement in infants at increased risk, including those with prematurity, hemolytic disease, early initiation of phototherapy, or bilirubin levels close to treatment thresholds, rather than routine testing in all neonates. Such an approach minimizes unnecessary blood sampling, reduces hospital stay, and optimizes resource utilization while ensuring safe follow-up of high-risk infants.

The present study has certain limitations. It was conducted at a single tertiary care center, which may limit the generalizability of the findings. Multivariable regression analysis could not be performed because of the limited number of rebound events. In addition, only short-term rebound after phototherapy was evaluated, and longer clinical follow-up was not undertaken. Nevertheless, the study provides valuable contemporary data on the incidence and risk factors

associated with rebound hyperbilirubinemia in Indian neonates and reinforces the importance of identifying high-risk infants who require closer monitoring after discontinuation of phototherapy.

Conclusion

Significant rebound hyperbilirubinemia occurred in 13.7% of neonates following phototherapy for unconjugated hyperbilirubinemia. Gestational age <38 weeks, birth weight <2500 g, ABO incompatibility, Rh incompatibility, early initiation of phototherapy, and higher bilirubin levels at discontinuation of phototherapy were significantly associated with rebound hyperbilirubinemia. Although G6PD deficiency was more frequent among neonates with rebound hyperbilirubinemia, the association was not statistically significant. These findings highlight the importance of identifying high-risk neonates before discharge and support selective post-phototherapy bilirubin monitoring rather than routine testing in all infants. Early recognition and appropriate follow-up of at-risk neonates may help prevent severe hyperbilirubinemia and its neurological complications.

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