SHORT COMMUNICATION

Bilirubin Rebound After Intensive Phototherapy for Neonatal Jaundice

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This study was conducted to determine the incidence and magnitude of post-phototherapy bilirubin rebound in neonates. Subjects included inborn neonates needing phototherapy for hyperbilirubinemia. Standard guidelines were used to start and stop phototherapy. Rebound bilirubin was measured 24±6 h after stopping phototherapy. Significant bilirubin rebound (SBR) was defined as post-phototherapy bilirubin level needing reinstitution of phototherapy. Among 245 neonates with hyperbilirubinemia, post-phototherapy bilirubin estimation was done in 232 neonates. A total of 17 (7.3%) neonates developed SBR. In neonates with SBR, bilirubin increased by 2.3 mg/dL (95% CI 1.6-3.0) after stopping phototherapy. Risk factors for SBR included birth at <35 weeks of gestation (RR 4.3, 95% CI 1.5-12.0), birthweight <2000 g (RR 3.2, 95% CI 1.0-10.3) and onset of jaundice at <60 h of age (RR 3.3, 95% CI 1.2-9.0). Post-phototherapy discharge and follow-up planning should take into account these risk factors.

Key words: *Bilirubin, Jaundice, Neonate, Phototherapy.*

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Intensive phototherapy in neonatal hyperbilirubinemia rapidly decreases serum total bilirubin (STB) below the threshold for treatment(1). However, underlying alteration in bilirubin production and excretion may persist and cause bilirubin rebound after stopping phototherapy. The need of measurement of bilirubin rebound after stopping phototherapy has been addressed previously by many observational studies(2-6). These studies have included neonates born at term or preterm gestation, those with or without positive direct Coombs test, and have concluded that significant bilirubin rebound is rare and therefore, measurement of bilirubin rebound is not needed. In addition, routine measurement of bilirubin rebound may increase workload, add to expenses and prolong the hospital stay. Despite evidence to contrary and guidelines of American Academy of Pediatrics on similar lines, measurement of bilirubin rebound after stopping phototherapy is a common practice(7). We conducted this study to determine the incidence and magnitude of post-phototherapy bilirubin rebound needing reinstitution of phototherapy.

METHODS

This study was conducted in the neonatal unit of a teaching referral hospital. Relevant information about inborn neonates needing phototherapy for hyperbilirubinemia during birth hospitalization or readmission from January 2008 to August 2008 was retrieved from case records. For neonates born at 35 or more completed weeks of gestation, the decision to start phototherapy was made on the basis of the age of the baby in hours and serum total bilirubin (STB) levels, as per American Academy of Pediatrics guidelines(7). In hemolytic jaundice, phototherapy was stopped when two consecutive STB levels were less than 14 mg/dL. In non-hemolytic jaundice, phototherapy was stopped when a single value of STB was less than 14 mg/dL. For

neonates born at less than 35 completed weeks of gestation or with birthweight less than 2500 g, phototherapy was initiated according to following level of STB: >5mg/dL in first 24 h of postnatal age, >10mg/dL or 0.8% of birthweight (whichever was lower) at 24-48 h and >15mg/dL or 0.8% of birthweight (whichever was lower) at >48 h of age. Phototherapy was stopped when STB fell 2 mg/dL below level at which phototherapy would be indicated for that age. As per unit policy, rebound bilirubin was measured 24±6 h after stopping phototherapy. Significant bilirubin rebound (SBR) was defined as post-phototherapy bilirubin level needing reinstitution of phototherapy.

Double-surface phototherapy was administered using special blue compact fluorescent tubes (Philips 20W TL 20/52). Irradiance of the phototherapy unit at level of skin of abdomen of the neonate was monitored once a day using a standard flux meter (Ginevri, Rome, Italy) sensitive to wavelengths of 425-475 nm. The tubes were replaced during the study period as and when they were visibly discolored or were producing less light or when the irradiance fell to less than 15 $\mu W/cm^2/nm$. To identify the underlying etiology, following investigations were conducted in all neonates requiring photo-therapy: direct Coombs test, ABO and Rhesus blood group if mother is of O blood group or is Rh negative, glucose-6-phosphate dehydrogenase (G6 PD) level, reticulocyte count and peripheral blood smear examination. STB was measured in biochemistry laboratory using automated analyzer.

Data entry and analysis were done using Epi-Info (CDC, Atlanta). Continuous data with normal distribution was analyzed by student *t*-test and non-normally distributed data by Mann-Whitney U test. Categorical data was analyzed by chi-square or Fisher exact test. *P* value of <0.05 was considered significant.

RESULTS

A total of 2609 neonates were born during the study period. Of these, 245 (9.4%) developed significant hyperbilirubinemia needing phototherapy and constituted the study cohort. Gestation at birth was less than 37 weeks in 134 (median gestation [IQR}: 34 [32-35] wk; mean birthweight [SD]: 1897 [587]g) and ≥37 weeks in 111 neonates (median gestation [IQR]: 38 [37-39] wk; mean birthweight [SD]: 2778 [480] g). Most common assigned etiology of jaundice was prematurity (55, 22.5%) followed by G6PD deficiency (17, 7%), ABO incompatibility (5, 2%), extravasated blood (3, 1.2%) and Rhesus incompatibility (2, 0.8%).

Post-phototherapy bilirubin estimation was done in 232 neonates. A total of 17 (7.3%, 95% CI 4.4-11.6) neonates developed significant bilirubin rebound. In neonates with SBR, bilirubin increased by 2.3 mg/dL (95% CI 1.6-3.0) after stopping phototherapy. Parity or age of mother, mode of delivery, positive direct Coombs test, G6PD deficiency and peak serum bilirubin were comparable in neonates with and without SBR. Risk factors for SBR included birth at <35 weeks of gestation (15.6% *vs* 4.2%, RR 4.3, 95% CI 1.5-12.0), birth weight<2000 g (10.8% *vs* 3.6%, RR 3.2, 95% CI 1.0-10.3) and onset of jaundice at <60 h of age (14.1% *vs* 4.8%, RR 3.3, 95% CI 1.2-9.0). Among neonates with absence of all these three risk factors, incidence of SBR was only 2.3% (2/86). Among neonates with presence of any one and all of the three risk factors, incidence of SBR was 10.3% (15/146) and 23.1% (6/26), respectively.

DISCUSSION

In the present study, we have reported the incidence of significant bilirubin rebound after stopping intensive phototherapy. Despite hyperbilirubinemia being a common morbidity among neonates, data about the phenomenon of bilirubin rebound is lacking. To the best of our knowledges this is the first report from India about incidence of SBR.

Previous reports in international literature have indicated that SBR is rare and therefore it is unnecessary to keep an infant in the hospital after phototherapy has been discontinued to check for SBR(2-5,8). Factors reported to influence incidence of SBR include proportion of premature neonates and hemolytic jaundice, severity and onset of hyperbilirubinemia, mode of feeding and presence of other risk factors like G6PD deficiency(6,9).

WHAT THIS STUDY ADDS?

- Significant rebound rise of bilirubin is observed in 10% neonates needing intensive phototherapy and the risk factors are gestation less than 35 weeks, birth weight <2000 gm and onset of phototherapy within 60 h of age.

In our study group, risk factors of SBR included gestation at birth<35 weeks, birth weight<2000 gm and onset of jaundice at <60 h of postnatal age. Incidence of G6PD deficiency in our study group (8.4%) was comparable with that of Kaplan, *et al*. who have also reported high incidence of SBR (8.7%). Rate of G6PD deficiency in neonates with SBR was higher than in those without SBR, although it did not reach statistical significance (13.3% *vs* 8%, *P*=0.36). Use of stricter criteria for stopping phototherapy may explain the lack of higher SBR in neonates with G6PD deficiency or positive direct Coombs test result.

Natural history of bilirubin levels after stopping phototherapy is still unclear. Management of hyperbilirubinemia in neonates is based on the principle of avoiding potentially 'neurotoxic' levels of bilirubin(10). Neurotoxic level of bilirubin may vary with postnatal age, maturity of blood-brain barrier, rate of rise of serum bilirubin, serum albumin concentration, presence of hemolysis and co-morbidities(10). The neurotoxic levels of bilirubin in late neonatal period, and whether untreated rebound bilirubin may reach those levels, are issues for further investigation.

We recommend that a rebound bilirubin level must be obtained in high-risk neonates (born at less than 35 weeks gestation or birthweight <2000 gm or onset of phototherapy within 60 h of age) 18-24 h after stopping phototherapy. Discharge may be delayed for this purpose if follow-up is not ensured.

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