Post-phototherapy neonatal bilirubin rebound: A potential cause of significant hyperbilirubinaemia

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Abbreviations
AAP American Academy of Pediatrics
G-6-PD glucose-6-phosphate dehydrogenase
PTB plasma total bilirubin
Abstract

Objective: To determine the incidence of post-phototherapy neonatal plasma total bilirubin (PTB) rebound.

Methods: A prospective clinical survey was performed on 226 term and near-term neonates treated with phototherapy in the well baby nursery of the Shaare Zedek Medical Center from January 2001 to September 2002. Neonates were tested for PTB 24 ± 12 hr after discontinuation of phototherapy, with additional testing as clinically indicated. The main outcome measure, significant bilirubin rebound, was defined as a post-phototherapy PTB ≥ 256 µmol/L. Phototherapy was not reinstituted in all cases of rebound, but rather according to clinical indications.

Results: 30 (13.3%) neonates developed significant rebound (mean (SD) PTB 287 ± 27 µmol/L, upper range 351 µmol/L). 22 of these (73%) were retreated with phototherapy at mean PTB 296 ± 29 µmol/L. Multiple logistic regression analysis demonstrated significant risk for aetiologic risk factors including positive direct Coombs’ test (Odds Ratio 2.44, 95% Confidence Interval 1.25-4.74, p=0.028) and gestational age <37 weeks (Odds ratio 3.21, 95% Confidence Interval 1.29-7.96, p=0.036). A greater number of neonates rebounded among those in whom phototherapy was commenced < 72 hours (26/152, 17%) compared with > 72 hours (4/74, 5.4%), Odds Ratio 3.61, 95% Confidence Interval 1.21 - 10.77.

Conclusion: Post-phototherapy neonatal bilirubin rebound to clinically significant levels may occur, especially in cases of prematurity, direct Coombs’ test positivity, and those treated < 72 hours. These risk factors should be taken into account when planning post-phototherapy follow up.
Introduction

Because the processes instrumental in the pathogenesis of the hyperbilirubinaemia may not yet have resolved by the time phototherapy is discontinued, post-phototherapy rebound may occur. However, data currently available are inadequate to formulate recommendations for or against post-phototherapy bilirubin testing. Many reports on the subject to date have been flawed by comprising retrospective chart reviews, analysis of rebound by determining the mean bilirubin value rather than peak post-treatment values, lack of preset definitions for rebound or indications for retreatment, pooling of data from term and extremely preterm neonates, or exclusion of neonates with haemolytic conditions from the analysis. [1][2][3][4][5][6]

The objectives of the study were 1. To determine the incidence of post-phototherapy rebound to a predefined bilirubin concentration. 2. To identify aetiologic factors for hyperbilirubinaemia that could be used to select infants at risk for rebound.

Methods

The study comprised an ongoing clinical survey of term and near-term neonates treated with phototherapy in the well baby nurseries of the Shaare Zedek Medical Center from January 2001 to September 2002. The Institutional Review Board of the institution gave approval for the study. Consecutively treated, otherwise healthy term and near-term infants (>35 weeks gestation) who had post-phototherapy plasma total bilirubin (PTB) determinations performed in our hospital's laboratory 24 ± 12 hours after discontinuation of phototherapy, were included. Excluded from this analysis were those neonates who had been treated in our nursery but who did not return to our facilities for their post-bilirubin follow-up.

Criteria for phototherapy for healthy term neonates were based on, but more stringent than, those of the 1994 American Academy of Pediatrics (AAP) Practice Parameter,[7] as follows: <24 hr: PTB 170 mol/L; 24-48 hr: 205 mol/L; 49-72 hr: 256 mol/L; >72 hr: 291-308 mol/L.

In infants with risk factors, including gestational age ≤37 weeks, direct Coombs' positivity, glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, Down syndrome, severe bruising, a strong family history of neonatal hyperbilirubinaemia or evidence of infection, phototherapy was started at PTB concentrations 1-2 mg lower than described above.

Criteria for readmission for primary treatment of hyperbilirubinaemia included PTB concentrations ≥308-342 µmol/L. Babies readmitted for primary or secondary (repeat) phototherapy were hospitalized in the same nursery in which they had been managed during their birth hospitalization.

Neonates were routinely evaluated for the following aetiological entities for their hyperbilirubinaemia using clinical data or employing standard laboratory tests: direct Coombs’ positive ABO blood group heterospecificity or other blood group isoimmunization, G-6-PD deficiency, direct Coombs’ negative ABO incompatibility, prematurity (gestational age ≤37 weeks), and breast feeding. Less common entities were evaluated according to clinical indications.
Phototherapy was provided with babies lying supine in open bassinets, using overhead blue 4 lamp fluorescent units (Medela Phototherapy Lamp, Medela Medical Technology, Baar, Switzerland) placed about 25 cm above the baby. In many instances a phototherapy mattress was used as well (BiliBed, Medela Medical Technology, Baar, Switzerland). Light intensity, measured at the level of the skin of the babies’ abdomen yielded a mean output of 17 ± 3 µW/cm²/nm (Minolta Fluoro-lite meter 451, Japan). Breast feeding was encouraged and discontinued only in selected infants in whom the PTB continued to rise to 342 µmol/L or more despite phototherapy. During phototherapy PTB levels were determined at least twice daily, and more frequently if deemed necessary by clinical assessment. Phototherapy was continued until the serum total bilirubin concentration decreased to below 205 µmol/L. In those cases of early hyperbilirubinemia in whom PTB concentrations did not exceed 205 µmol/L, treatment was discontinued when PTB concentrations stabilized and became lower than the 75th percentile on the hour of life specific bilirubin nomogram. [8]

Protocol for post-phototherapy rebound: Nursery protocol includes a post-phototherapy PTB determination 24 ± 12 hours after discontinuation of phototherapy, but does not require babies to remain hospitalized. Those neonates whose post-phototherapy PTB concentration was lower than that at the time of discontinuation of phototherapy were discharged from follow-up. Those in whom the repeat PTB was ≥120% of the post phototherapy PTB, or ≥239 µmol/L, were followed up at 12-24 hr intervals until either stabilization/decrease of the PTB concentrations, or reinitiation of phototherapy. Phototherapy was recommenced at the discretion of the attending neonatologist, but not usually at PTB values < 256 µmol/L. The decision to reinstitute phototherapy was influenced by the presence of risk factors for hyperbilirubinemia.

Data analysis: Significant post-phototherapy rebound was arbitrarily defined, for the purpose of the study, as a PTB concentration that had risen to ≥256 µmol/L in a neonate who had been treated under phototherapy according to our protocol (See discussion).

The number of neonates with post-phototherapy PTB rebound ≥256 µmol/L was determined. The highest post-phototherapy PTB was noted, although this was not always equivalent to the natural peak, depending on the reinstitution of phototherapy. The number of neonates retreated with phototherapy was recorded. The fact that a baby did develop rebound according to our definition, did not necessarily imply that that baby was retreated with phototherapy. To determine which aetiological groups were at significant risk for rebound hyperbilirubinemia, data were further analysed by comparing rebound between aetiological conditions including direct Coombs' positivity, prematurity, G-6-PD deficiency, ABO blood group incompatibility with negative direct Coombs' test, and breast feeding as the only aetiology, using multiple logistic regression analysis. Early institution of phototherapy (≤ 72 hrs) was compared with those with later onset using Odds Ratio and 95% Confidence Intervals.

Continuous variables were compared using Student’s t test and categorical variables were compared by using χ² analysis. Significance was defined as a p value <0.05 or, in the case of Odds Ratio determination, a 95% confidence interval that did not include the digit 1.

Estimation of sample size: Presuming equal numbers of neonates with hemolytic and non-hemolytic conditions, a 15% rate of rebound in the hemolytic group, and a 5% rate in the non-hemolytic group, with a power of 0.8 and an alpha value of 0.05, it was estimated that a
total of 160 patients would be necessary to compare babies with increased hemolysis with those who did not have hemolysis.

Laboratory methods: PTB was measured routinely in the hospital’s clinical biochemistry laboratory by a direct spectrophotometric method using spun capillary tube samples (Wako Bilirubin Tester, Wako Pure Chemical Industries, Ltd., Osaka, Japan).

Direct Coombs testing and G-6-PD screening were performed by routine laboratory methods.

Results

A total of 312 neonates was treated with phototherapy during the study period. Of these 226 (72%) returned for follow-up at our Medical Center and were thus eligible for inclusion. Mean ± SD values for birth weight and gestational age were 3204 ± 445 gm and 39 ± 2 weeks, respectively. Two hundred and six (91%) were born vaginally, and the male:female ratio was 134:92. Two hundred (88.5%) neonates were either totally or partially breastfeeding. Thirty of the 226 (13%) were readmitted for primary phototherapy: demographic data did not differ significantly between those receiving primary phototherapy during their birth hospitalisation and those readmitted.

Of the 196 neonates who received primary phototherapy during their birth hospitalization, 110 (56%) had a positive direct Coombs’ test (106 were ABO heterospecific, 3 had anti-e and 1 anti-c isoimmunization, and 1 required exchange transfusion). Forty-three (21.9%) were ≤ 37 weeks gestation, 17 (8.7%) G-6-PD deficient, and 20 (10.2%) were ABO heterospecific with a negative direct Coombs’ test. (Some overlap occurred between entities). In the subgroup of 30 neonates rehospitalized for primary phototherapy, all of whom were breast feeding, 6 (20%) were ≤ 37 gestational weeks, 2 (6.6%) were direct Coombs positive, 5 (16.6%) were G-6-PD deficient and 5 (16.6%) were ABO incompatible but with a negative direct Coombs test. Data regarding PTB values at onset and discontinuation of phototherapy, and the number of neonates with significant bilirubin rebound in both subgroups, are presented in Table 1.

<table>
<thead>
<tr>
<th>Primary phototherapy during birth hospitalization (n=196)</th>
<th>Primary phototherapy during readmission (n=30)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (hr, mean ± SD)</td>
<td>53 ± 29</td>
<td>122 ± 38</td>
</tr>
<tr>
<td>PTB at onset (µmol/L)</td>
<td>251 ± 53</td>
<td>318 ± 22</td>
</tr>
<tr>
<td>Age at discontinuation</td>
<td>96 ± 25</td>
<td>152 ± 40</td>
</tr>
<tr>
<td>PTB at discontinuation</td>
<td>182 ± 20</td>
<td>182 ± 18</td>
</tr>
<tr>
<td>Duration of phototherapy (hr)</td>
<td>43 ± 23</td>
<td>30 ± 9</td>
</tr>
<tr>
<td>Number of neonates rebounding to PTB ≥ 256 µmol/L</td>
<td>30 (15.3%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 1. Data comparing onset and discontinuation of phototherapy, and the number of neonates with significant bilirubin rebound, between the two subgroups receiving primary phototherapy during birth hospitalization and readmission hospitalization, respectively.
Overall, 30 (13.2%) neonates had post-phototherapy PTB concentrations which rebounded to \( \geq 256 \mu\text{mol/L} \). The mean (SD) PTB value of the rebounding neonates was 298 ± 29 \( \mu\text{mol/L} \). The highest PTB concentration noted was 351 \( \mu\text{mol/L} \), while in 3 neonates rebound PTB value exceeded 342 \( \mu\text{mol/L} \). The number of neonates rebounding in each etiologic subgroup were compared using multiple logistic regression analysis: of all the etiologic subgroups studied, significance was demonstrated only for those with a positive direct Coombs’ test (Odds Ratio 2.44, 95% Confidence Interval 1.25-4.74, \( p=0.028 \)) and gestational age \(< 37 \) weeks (Odds ratio 3.21, 95% Confidence Interval 1.29-7.96, \( p=0.036 \)). Furthermore, a greater number of neonates rebounded among those in whom phototherapy was commenced \(< 72 \) hours (26/152, 17%) compared with \( > 72 \) hours (4/74, 5.4%), Odds Ratio 3.61, 95% Confidence Interval 1.21-10.77.

Of the 30 neonates with significant rebound, 22 (73%) were retreated with phototherapy, of whom 15 were still hospitalized during birth hospitalization and 7 were readmitted. Of those babies who received secondary phototherapy, 16 were direct Coombs’ test positive, 5 were \(< 37 \) weeks gestation, and 1 was G-6-PD deficient. Secondary phototherapy was commenced 42 ± 26 hours after discontinuation of the initial phototherapy (2 neonates were retreated with phototherapy \(< 24 \) hr after first discontinuation). Mean PTB at onset of repeat phototherapy was 296 ± 29 \( \mu\text{mol/L} \).

Discussion

Few studies have systematically related to the phenomenon of post-phototherapy rebound.[1][2][3][4][5][6] Yetman et al [1], pooling term as well as premature and low birth weight neonates, found mean bilirubin levels at the time of rebound testing were significantly lower than at discontinuation of phototherapy, but did not supply information regarding peak rebound bilirubin concentrations. Significant rebound was not defined by preset criteria, and only the first serum bilirubin determination performed within 30 hours of phototherapy was included in their analysis. Lazar et al [2], followed serum bilirubin levels to their natural peak in term neonates with non-haemolytic hyperbilirubinemia. The upper range of rebound bilirubin reached a peak of 267 \( \mu\text{mol/L} \). However, the data from this series cannot be extrapolated to neonates with haemolytic conditions. Maisels and Kring [3] used an episode of repeat phototherapy as an index of bilirubin rebound, although in this study preset criteria for repeat phototherapy were not set. Secondary phototherapy was instituted in 8.2% of those who received early treatment during their birth hospitalisation, compared with only 0.7% of those readmitted for primary phototherapy. In some cases the serum bilirubin did rise \( > 342 \) \( \mu\text{mol/L} \). Al_Saedi [4] followed neonates for 8.3 ± 5.3 hours post-phototherapy and documented decrease in mean post-phototherapy bilirubin concentrations, although upper limits of the rebound were not provided. Erdeve et al [5] found that bilirubin concentrations that did not increase significantly in 375 neonates followed for up to 12 hours after discontinuation of phototherapy, although 5.1% of these neonates did have repeat phototherapy. However, neither the upper limit of the rebound range or the criteria for repeat phototherapy in that study were stated. Del Vecchio et al studied 48 neonates, of whom one 36 week gestation infant was retreated with phototherapy for a rebound bilirubin level of 17.0 mg/dL [6]. Brown et al [9] found minimal increase in serum bilirubin concentrations in \(< 2000\)gm birth weight infants treated with prophylactic phototherapy, but in babies \( > 2000 \)gm birth weight, treated only if they actually developed hyperbilirubinemia, STB values continued to decline once phototherapy was discontinued. Tan et al [10] found that only
7.89 per 1000 neonates required retreatment with phototherapy although, again, preset criteria were not established.

In contrast, our patients were treated according to preset guidelines. Significant rebound was strictly defined, and neonates were analyzed according to etiological subgroup. Neonates with haemolytic conditions were included, and upper limits of rebound bilirubin documented. Rebound occurred in 13.2% of neonates, and exceeded 342 µmol/L, a level of bilirubin of concern in patients with haemolysis, in several cases. At highest risk were premature infants or those with a positive direct Coombs’ test. The increased risk associated with those in whom phototherapy was instituted within the first 72 hours of life probably reflects the higher number with active haemolysis within this subgroup. No subgroup was exempt from significant rebound except for those rehospitalised for primary phototherapy. The explanation for this may that few babies in the rehospitalisation group had haemolytic conditions, and, as a result of their older age, by the time phototherapy is discontinued, the natural postnatal rise in bilirubin will have levelled off, concomitant with maturation of the bilirubin conjugation process.

We pre-defined significant rebound as a PTB concentration of \( \geq 256 \) µmol/L as this represented a 25% increase over our routine indication for discontinuation of phototherapy (205 µmol/L) and is the beginning of the range of the 95th percentile for bilirubin after the first 2-3 days of life.\[1\] Our definition of rebound should not necessarily be equated with danger nor with a decision to reinstitute phototherapy. However, there were instances in which the rebound PTB value exceeded 342 µmol/L, a bilirubin concentration which may be considered dangerous to actively haemolysing neonates or those <37 weeks gestation.

Because of the logistics involved in comprehensive follow-up, and for accuracy and standardization, we included in our analysis only those neonates tested for rebound in our hospital’s laboratory. There was no reason to suspect that those babies who were followed up elsewhere were different from those included in this study. Our 72% retrieval rate does supply a reasonable reflection of the number of neonates affected by rebound and the drop out should not have resulted in substantial bias.

The 1994 Practice Parameter of The American Academy of Pediatrics (AAP), which was applicable at the time this study was being performed, but not applicable to neonates with haemolytic conditions, recommended that in most cases no further measurement of bilirubin is necessary following discontinuation of phototherapy, except possibly for cases in which phototherapy was instituted early and discontinued before the infant was 3 or 4 days old.\[1\] The subsequent (2004) recommendations suggest that discharge from hospital need not be delayed in order to observe an infant for rebound.\[12\] The AAP Subcommittee on Hyperbilirubinemia now recommends a follow-up bilirubin measurement within 24 hours of discharge for those cases in which phototherapy was used for neonates with haemolytic diseases, initiated early or discontinued before the infant is 3 to 4 days old. The Committee regards significant rebound among neonates who had been rehospitalised for hyperbilirubinaemia to be a rare occurrence and suggests a bilirubin measurement or clinical evaluation after 24 hours in these infants as a clinical option.

In light of our data, we recommend risk assessment in the selection of neonates to be tested for rebound hyperbilirubinaemia. Neonates with Coombs' positive isoimmunization, borderline prematurity, onset of phototherapy \( \leq 72 \) hours, or a post-phototherapy rate of bilirubin rise greater than expected for age in hours, should be regarded as high risk. On the
other hand, babies readmitted for primary phototherapy appear to be at low risk. No set of recommendations can be all-encompassing. Post-phototherapy bilirubin follow up should be incorporated using a combined approach of individualization, evaluation of risk factors, and application of common sense.

**Competing interests**
None declared

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**What is already known on this subject**
Post-phototherapy bilirubin rebound to bilirubin levels which may be of concern does occur. However, the incidence of post-phototherapy rebound, defined prospectively, has not been adequately studied. Studies to date have been flawed due to retrospective nature of patient data reviews, use of mean bilirubin values without supplying peak rebound values, pooling of term and preterm infants, exclusion of neonates with haemolytic conditions, and introduction of secondary phototherapy without a predefined protocol.

**What this study adds**
In the current study, patients were treated by phototherapy according to preset guidelines. Significant rebound was prospectively defined, and risk factors for rebound were analysed according to etiological subgroup. Neonates with haemolytic conditions were included, and upper limits of bilirubin rebound, prior to reinstitution of phototherapy where applicable, documented. This study demonstrates that neonates <37 weeks gestation, those with direct Coombs’ test positivity, and those treated ≤ 72 hours, are at high risk for significant post-phototherapy rebound.
References

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