When should phototherapy be stopped? A pilot study comparing two targets of serum bilirubin concentration

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Abstract
Objective: The objective of this study was to compare the outcome of two groups of jaundiced newborns randomized to one of the two targets of total serum bilirubin (TSB) for phototherapy discontinuation.

Design: Infants treated with phototherapy were assigned to two groups: in the ‘high-threshold’ group, phototherapy was interrupted when TSB decreased to ≥1 mg/dL (17 μmol/L) below the limit requiring phototherapy and in the ‘low-threshold’ group when TSB decreased to ≥3 mg/dL (51 μmol/L) below the same limit.

Results: Fifty-two infants were enrolled, 25 in the high- and 27 in the low-threshold group. Phototherapy duration was significantly shorter in the high- than in the low-threshold group (22.3 ± 13 vs. 27.6 ± 12 h, respectively, p = 0.03). Length of hospital stay was 84±30 h in the high- and 94 ± 24 h in the low-threshold group (p = 0.05). Additional phototherapy was required in 20% of the high- versus 18% of the low-threshold group (p = 0.58). In the presence of haemolysis or G6PD deficiency, 28% of the infants required re-phototherapy and 8.3% when such factors were absent (p = 0.06).

Conclusion: Phototherapy duration may be shortened by using higher TSB limits for interruption. When hyperbilirubinaemia is accompanied by risk factors, the infants should be followed for longer periods, since some of them will need re-phototherapy.

INTRODUCTION
In July 2004, the subcommittee for hyperbilirubinaemia of the American Academy of Pediatrics (AAP) published new clinical guidelines regarding neonatal jaundice (1). These guidelines did not include specific recommendations about the total serum bilirubin (TSB) concentrations at which phototherapy may be discontinued, except for infants readmitted after discharge from their birth hospitalization, for whom discontinuation of phototherapy was recommended whenever the TSB drops below 13–14 mg/dL (222–239 μmol/L). This recommendation cannot be applied to younger infants during their birth hospitalization for whom the phototherapy is sometimes started at lower TSB concentration (1).

The aim of the present study was to compare the outcome of two groups of jaundiced but otherwise healthy newborns randomized to one of the two targets of bilirubin concentration for discontinuation of phototherapy. One of the two targets was 1 mg/dL (17 μmol/L) or more below the threshold for phototherapy initiation (high-threshold group), and the second one was 3 mg/dL (51 μmol/L) or more below the same threshold (low-threshold group). We hypothesized that earlier interruption of phototherapy increases the need for an additional course of phototherapy and ultimately prolongs the length of hospital stay. We elected to conduct a pilot study of approximately 50 infants in order to determine the final sample size of a potentially larger study.

METHODS
Study design
This randomized clinical trial was performed between November 2004 and March 2005 in the well newborn nursery of ‘Lis’ Maternity Hospital, Tel Aviv Sourasky Medical Center. Eligible for enrollment were healthy infants delivered above 36 weeks of gestation and weighing over 2500 g. Infants were recruited consecutively whenever one of the authors (M.B.) was attending in the normal newborn nursery. The study was approved by the local Institutional Review Board and written informed consent was obtained from both parents of each infant.

In our institution, most infants are discharged at or around 48 h of age and about 80% of them (all those felt to be jaundiced, even slightly) have at least one pre-discharge TSB concentration measured. In rare cases, when infants are discharged earlier than 48 h of age, they are scheduled for a repeated TSB measurement on the following day in our laboratory.
Whenever a child met the AAP guidelines criteria for phototherapy (1), his/her parents were contacted, and written informed consent was obtained for the study, which was approved by our local Institutional Review Board. The infants were then randomized to one of the two groups: in the first one (high-threshold group), phototherapy was to be discontinued whenever TSB would decrease to ≥1 mg/dL (17 μmol/L) below the phototherapy threshold of AAP guidelines, as they appear in the AAP published nomogram (1). In the second group (low-threshold group), phototherapy was to be discontinued whenever TSB would decrease to ≥3 mg/dL (51 μmol/L) below the phototherapy threshold of the AAP guidelines. The randomization was performed by computer-generated numbers, in blocks of six. The sequence was concealed until the infant had been assigned to one of the two groups.

Parents of the infants were blinded as to the randomization group of the infants, but the physician team taking care of the babies was not. Laboratory technicians involved in the measurement of TSB were blinded as to the allocation of the infants.

By design, between 6 and 12 h after phototherapy has been stopped, a blood sample was obtained for TSB measurement. Infants were discharged whenever no significant rise in TSB concentration had been detected and re-invited for another TSB measurement, whenever possible, at about 24 h after phototherapy was discontinued. A rise in TSB concentration was considered significant whenever it entered the zone predicting the need for further phototherapy, using the same AAP nomogram relevant to the age of the infant at the repeat TSB sampling (1).

All infants were cared for in open bassinets and phototherapy was administered continuously with 2–3 fluorescent lamps (Medela Medical Technology, Baar, Switzerland), each one including four 18 W fluorescent tubes, blue and white light. In a preliminary study, we found that, when placed the closest possible to the infant’s skin surface, the average irradiance at the skin surface generated by the three lamps was 22–25 μW/cm²/nm (15.73 ± 5.54 μW/cm²/nm), as measured with a Minolta/Air-Shields fluoro-lite Meter 451.

The following laboratory investigations were performed in each of the infants before the phototherapy treatment had been started: total and conjugated bilirubin concentration, complete blood count, reticulocytes count, blood group and direct Coombs test, and the G6PD quantitative assay using quantitative colorimetric method of reduction of NADPH+ (Sentinel CH, Milan, Italy) (2). TSB concentration was monitored every 6–8 h throughout the phototherapy course using a photometrically monitored reaction (Advia 1650 Bayer, USA).

Outcome measures
In order to confirm group comparability, the following data were collected: birth weight, gestational age, gender, presence of a risk factor for developing hyperbilirubinaemia like a positive direct Coombs test, G6PD deficiency, scalp haematomas and exclusive breast feeding.

The primary outcome measures were duration of phototherapy and hospitalization, TSB rebound at about 12 and 24 h after termination of phototherapy need for reinstitution of phototherapy, and length of hospital stay.

Statistical analyses
Sample size
We elected to conduct a pilot study of approximately 50 infants in order to determine the final sample size of a potentially larger study.

Differences between the two randomization groups were studied using the Student t-test for normally distributed variables and Kruskal–Wallis tests for non-parametric variables. Length of stay (LOS) in the hospital is not normally distributed and was expressed as a rank. We used logistic regression analysis to study the effect of the randomization group, the presence or not of risk factors for haemolysis, the gender and the gestational age upon the need for a second course of phototherapy.

A p-value of <0.05 was considered significant.

RESULTS
There were 78 infants that fulfilled the criteria for inclusion in the study. Of them, 25 were not enrolled, because of parental refusal (3) or because parents could not reach in time for inclusion (4). Thus 53 infants remained in the study, of which 26 were randomized to the high-threshold group and 27 in the low-threshold group. One infant in the high-threshold group was later lost to follow-up. Three infants in each one of the two groups did not undergo the second rebound bilirubin-check test at the age of 24 h after phototherapy interruption.

Table 1 depicts selected clinical and laboratory characteristics of the study infants. Briefly, both groups were comparable for all demographic parameters.

Table 2 depicts TSB concentrations at the time of phototherapy initiation and interruption, as well as the TSB rebound (expressed as the difference between TSB concentration at the time phototherapy was interrupted and TSB concentration measured at follow-up). It also depicts relevant follow-up clinical data such as phototherapy duration, length of hospital stay and the need or not for an additional course of phototherapy. Mean TSB concentration

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Selected clinical and laboratory characteristics of the study infants.</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>High-threshold group (n = 25)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3324 ± 434</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>38.9 ± 1.4</td>
</tr>
<tr>
<td>Male sex</td>
<td>13 (52%)</td>
</tr>
<tr>
<td>Exclusively breast-fed</td>
<td>14 (56%)</td>
</tr>
<tr>
<td>Positive direct Coombs test</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>G6PD deficient</td>
<td>5 (18.5%)</td>
</tr>
<tr>
<td>Scalp haematomas</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Weight loss &gt;10%</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Data are mean ± SD or n (%).
Table 2 Total serum bilirubin concentrations (μmol/L) at the initiation and discontinuation of phototherapy and rebound TSB at a mean of 10 and 28 h.

<table>
<thead>
<tr>
<th></th>
<th>High-threshold group</th>
<th>Low-threshold group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSB at phototherapy initiation</td>
<td>241.1 ± 54.7</td>
<td>261.6 ± 56.4</td>
<td>0.167</td>
</tr>
<tr>
<td>Difference between infant TSB at initiation of phototherapy and AAP-recommended level</td>
<td>21.55 ± 19.67</td>
<td>16.93 ± 24.97</td>
<td>0.186</td>
</tr>
<tr>
<td>Infant TSB on discontinuation of phototherapy and AAP-recommended level for initiation of phototherapy</td>
<td>229.14 ± 30.78</td>
<td>218.88 ± 41.04</td>
<td>0.640</td>
</tr>
<tr>
<td>Difference between infant TSB at discontinuation of phototherapy and AAP-recommended level</td>
<td>28.73 ± 12.31</td>
<td>69.60 ± 17.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time (h) between phototherapy discontinuation and first TSB rebound measurement</td>
<td>11.0 ± 4.3</td>
<td>9.5 ± 3.2</td>
<td>0.33</td>
</tr>
<tr>
<td>Time (h) between phototherapy discontinuation and second TSB rebound measurement</td>
<td>28.2 ± 10.5</td>
<td>27.5 ± 7.9</td>
<td>0.84</td>
</tr>
<tr>
<td>TSB rebound at 10 ± 3.7 h</td>
<td>1.88 ± 25.65</td>
<td>4.79 ± 22.23</td>
<td>0.96</td>
</tr>
<tr>
<td>(−49.59–42.75)</td>
<td>(−46.17–64.98)</td>
<td></td>
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</tr>
<tr>
<td>TSB rebound at 28 ± 10 h</td>
<td>19.15 ± 29.07</td>
<td>11.63 ± 36.42</td>
<td>0.24</td>
</tr>
<tr>
<td>(−46.17–75.24)</td>
<td>(−47.88–83.79)</td>
<td></td>
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<tr>
<td>Duration of phototherapy (h)</td>
<td>22 ± 13</td>
<td>27 ± 12</td>
<td>0.031</td>
</tr>
<tr>
<td>Length of hospital stay (h)</td>
<td>84 ± 29</td>
<td>94 ± 24</td>
<td>0.05</td>
</tr>
<tr>
<td>Infants requiring additional course of phototherapy, n (%)</td>
<td>5 (20)</td>
<td>5 (18)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Data are given as mean (μmol/L) ± SD and range (in parenthesis). To convert TSB values to mg/dL divide by 17.1.

At phototherapy initiation was similar between the high-threshold group and the low-threshold group. TSB concentration above the AAP-recommended level for initiation of phototherapy was also similar between groups. As expected, and by design, at the time phototherapy was interrupted, TSB concentration below the recommended level for initiation of phototherapy was significantly lower in the low-threshold group than in the high-threshold group (p < 0.001). However, there was no significant difference in mean TSB concentration between groups at discontinuation of phototherapy. The time after discontinuation of phototherapy until TSB-rebound measurement was similar between randomization groups (Table 2). There were no significant differences between the groups in terms of rebound TSB values, neither at an average of 10 h nor at an average of 28 h post-phototherapy interruption. However, the duration of the phototherapy treatment was significantly shorter in the low-threshold group, as compared with the high-threshold group (a difference averaging approximately 5 h, significant at a p-value of 0.03 and a power of 0.52).

Similarly, the length of hospital stay was significantly shorter (by an average of 10 h) in infants of the high-threshold, as compared to the low-threshold group (p = 0.05). Five out of 25 infants in the high-threshold group (20%) and 5 out of 27 infants in the low-threshold group (18%) needed a second course of phototherapy (p = 0.58). When compared with those infants who did not require additional phototherapy, there were no significant differences in TSB at the start of phototherapy (13.7 ± 2.7 mg/dL vs. 15.3 ± 3.4 mg/dL (234.3 ± 46.2 μmol/L vs. 261.6 ± 58.1 μmol/L), p = 0.43), or in TSB above the phototherapy threshold (1.6 ± 1.3 mg/dL vs. 1.0 ± 1.3 mg/dL (27.4 ± 22.2 μmol/L vs. 17.1 ± 22.2 μmol/L), p = 0.17). The length of hospital stay was significantly prolonged in those infants who necessitated an additional course of phototherapy (117 ± 31 h vs. 82 ± 22 h, p < 0.001). More infants, eight out of 28 (28%) required a second course of phototherapy when they had a positive Coombs test, or G6PD deficiency, or scalp haematomas, compared with only 2 out of 24 (8.3%) of those without such haemolysis risk factors (p = 0.066).

In logistic regression analysis taking into account the need for a second course of phototherapy (dependent variable) and the randomization group, the presence or not of the above-mentioned haemolysis risk factors, gender and gestational age (independent variables), only the presence or not of haemolysis risk factors influenced (at the border of statistical significance) the need for a second course of phototherapy (R² = 6.55, p = 0.067).

**DISCUSSION**

Phototherapy is widely accepted as a standard method for the management of neonatal hyperbilirubinaemia and has minimal adverse effects (4–13). The American Academy of Pediatrics Subcommittee for Hyperbilirubinaemia left the decision of discontinuing phototherapy at the discretion of the physicians, depending ‘on the age at which the phototherapy is initiated and the cause of hyperbilirubinaemia’.

The medical literature is scant on recommendations for phototherapy interruption. Tan (14) advised to use a threshold of <11 mg/dL (185 μmol/L) (a value close to the mean of 170 μmol/dL, the mean TSB concentration in healthy infants).
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full-term Singapore babies) for termination of phototherapy. Lazar et al. (15) used higher limits than those recommended by Tan (13 ± 0.7 mg/dL in term infants and 10.7 ± 1.2 mg/dL in preterm infants) and showed the existence of a TSB concentration rebound of less than 1 mg/dL average. The study by Lazar did not include babies with haemolytic conditions. On the other hand, Kaplan et al. showed that babies with haemolytic conditions (Coombs positive) did rebound to a greater extent than others (16). The AAP recommended in 1994 that phototherapy may be discontinued in the term, healthy newborn when TSB level falls bellow 14–15 mg/dL (239.4–256.5 μmol/L) (17) but did not confirm this recommendation in 2004 (18).

Although very preliminary, our study is unique in two aspects: (1) it is the first one that compares the evolution of hyperbilirubinaemia at two targets of bilirubin concentration for phototherapy cessation conducted in a prospective, randomized clinical trial, and (2) it is the only one that used the AAP nomograms (1) that allow to individualize a threshold concentration for phototherapy cessation (taking into account the infant's age and the presence of risk factors such as haemolytic disease, prematurity, etc.) rather than a universal number for all infants.

In our study, adopting a higher threshold for termination of phototherapy > 1 mg/dL (17 μmol/L) below the limit indicating need for phototherapy led to a significant reduction of both phototherapy duration (by an average of 5 h) and length of stay (by an average of 10 h), without significantly affecting rebound TSB values. A few studies failed to show a significant TSB rebound after stopping phototherapy (3,15,19). In contrast, the present study showed that late (24 h or more after phototherapy interruption) rebound might occur. Many such infants (28% of those with haemolysis risk factors, and 8.3% of those without) even required an additional course of phototherapy. A possible reason for the apparent discrepancy between the above-mentioned studies and ours might reside in the fact that we followed up these infants for a longer period (average 28.6 ± 10.0 h) than others (12.5–17.6 h) (3,15,19–21).

An obvious limitation of our study is its relatively small sample size. As stated earlier, this study is a pilot one that was designed essentially to help us determine the sample size of a larger, more definitive study. From the fact that infants with risk factors and those without behave differently, we will have, in our planned larger study, to recruit enough infants in each group (with and without risk factors) in order to conduct separate analyses, as conclusions may differ between these two groups.

Another limitation of this study was the lack of blinding of the clinicians involved in this study. We do not believe that the lack of clinicians’ blinding may have influenced some kind of bias, since after randomization, all clinical decisions were made according to a very strict algorithm, and that deviations from it were not allowed.

As mentioned in the Results section, 20% of the infants treated for a longer period (low-threshold group) had a TSB rebound requiring a new phototherapy course, while only 18% of those receiving a shorter course (high-threshold group) received an additional one. It is theoretically possible that the lack of statistical significance between 20% and 18% was due to too small a sample size (type II error).

However, if this difference were true, it would probably be of little clinical significance.

In logistic regression analysis taking into account the need for a second course of phototherapy, the presence or not of haemolysis risk factors influenced nearly significantly (p = 0.067) the need for a second course of phototherapy, while the randomization group was not influential. If confirmed by a larger study, this finding may indicate that the cause of the jaundice and not the phototherapy duration determines an increased risk for significant rebound hyperbilirubinaemia and, therefore, the need for an additional course of phototherapy.

In conclusion, we showed that the duration of phototherapy might be shortened by using higher TSB concentration limits for interruption of phototherapy. Whether this might significantly increase the risk of bilirubin rebound may only be demonstrated in a much larger study. Our study does not allow us to determine whether infants with risk factors such as increased haemolysis or by G6PD deficiency should be treated for longer periods of time or alternatively followed for longer periods after phototherapy is stopped. In view of the results of our study, it seems that the need for reinstitution of phototherapy cannot be avoided by unduly prolonging the first phototherapy course.

References


