Trends of Transcutaneous Bilirubin in Neonates Who Develop Significant Hyperbilirubinemia

abstract

OBJECTIVES: To provide data on the natural course of transcutaneous bilirubin (TcB) levels in neonates before the development of significant hyperbilirubinemia, and to assess the effect of different demographic and perinatal factors on the rate of TcB increase.

METHODS: We analyzed 2454 TcB measurements from 419 neonates before the development of significant hyperbilirubinemia. Mean TcB values and TcB percentiles for designated times were calculated, and the effect of different risk factors on the rate of TcB increase was assessed. TcB percentile curves were plotted for comparison on a population-based TcB nomogram.

RESULTS: Blood incompatibilities and glucose-6-phosphate dehydrogenase deficiency were associated with higher rates of TcB increase during the first 36 to 48 postnatal hours, whereas smaller gestational age, increased weight loss, and exclusive breastfeeding had a similar but later effect. Compared with general population norms, a different pattern of TcB increase was noted in neonates who developed significant hyperbilirubinemia, but with a substantial overlap of TcB values during the first 24 to 48 postnatal hours.

CONCLUSIONS: We provide data on the natural course of TcB levels before the development of significant hyperbilirubinemia in a white population of term and near-term neonates. Smaller gestational age, blood incompatibilities, glucose-6-phosphate dehydrogenase deficiency, increased weight loss, and exclusive breastfeeding significantly affected the rate of TcB increase in a time-dependent manner. These findings may assist in assessing the risk for significant hyperbilirubinemia and planning appropriate follow-up strategies for neonates with borderline bilirubin levels. Pediatrics 2012;130:e898–e904
In the era of early discharge from nurseries and maternity units, prompt detection of neonates at risk for developing significant hyperbilirubinemia has become particularly challenging. On this premise, hour-specific evaluation and predischarge risk assessment of bilirubin levels according to the 2004 American Academy of Pediatrics (AAP) practice guidelines, has proved effective in reducing the incidence of severe jaundice. In the same guidelines, transcutaneous bilirubin (TcB) was recommended as an alternative to total serum bilirubin (TSB) for screening jaundiced neonates; and because transcutaneous bilirubinemia (TcB) was recommended as an alternative to total serum bilirubin (TSB) for screening jaundiced neonates; and because transcutaneous bilirubinometry minimizes invasive blood sampling and allows for a time-effective and reasonably accurate estimation of bilirubin levels, the method has become particularly popular among health care professionals involved in neonatal care.

In recent years, several TcB nomograms have been developed in an attempt to incorporate transcutaneous bilirubinometry into daily clinical practice. Using such population-based nomograms, significant hyperbilirubinemia is usually defined as a TcB value that exceeds the 95th hour-specific percentile. However, current evidence suggests that there is an important overlap of TcB values between neonates who will and those who will not develop significant hyperbilirubinemia, an overlap that could, and seems to, limit the predictive ability of percentile-based nomograms, especially during the first 24 to 48 postnatal hours. In this context, knowledge of the natural course of bilirubin levels in neonates who ultimately develop significant hyperbilirubinemia would be extremely useful, as it could allow for the earlier identification and appropriate follow-up of these infants. Data on TcB trends in neonates who require phototherapy are sparse, however, because these neonates were either excluded or not separately analyzed in most relevant studies.

The aim of the current study was to provide data on the natural course of TcB values in term and near-term neonates before the development of significant hyperbilirubinemia. We also sought to examine the effect of different demographic and perinatal factors on bilirubin increment rate, and to assess the pattern of TcB increase in these neonates in comparison with general population norms.

METHODS

Study Population

This prospective cohort study was performed at the well-infant nursery of the University Hospital of Patras (Patras, Greece) from September 2006 to August 2011. All neonates with gestational age ≥35 weeks and birth weight ≥2000 g who developed significant hyperbilirubinemia and required phototherapy during their hospital stay or after discharge were eligible to participate in the study. Significant hyperbilirubinemia was defined as a TSB value that exceeded the hour-specific threshold for phototherapy according to the AAP guidelines. Neonates admitted to the NICU and those with hyperbilirubinemia who required intervention within the first 24 hours were excluded.

The study was approved by the local ethics committee, and informed consent was obtained from 1 of the parents. The assignment of any medical intervention (including TSB measurements and decision for phototherapy) was strictly adhered to the guidelines applied in our nursery for the management of neonatal jaundice.

Protocol

Because our institution applies a discharge policy of ≥72 hours for healthy infants delivered vaginally and ≥96 hours for those having cesarean delivery, additional outpatient follow-up that involves repeat TcB (and if needed TSB) measurements is offered to all jaundiced infants. Neonates who develop significant hyperbilirubinemia before discharge receive phototherapy in the well-infant nursery. Those who develop significant hyperbilirubinemia after discharge are admitted to our Pediatric Department. Thus, neonates participating in this study had serial TcB measurements at regular time intervals of 12 ± 2 hours until the development of significant hyperbilirubinemia and initiation of phototherapy. TcB values were recorded on a special flow sheet attached to the medical file of each infant. Only TcB measurements obtained at ≥12, 18 ± 2, 24 ± 4, 36 ± 4, 48 ± 4, 60 ± 4, 72 ± 4, 96 ± 4, 108 ± 6, and 120 ± 6 hours were considered in the current study. Measurements obtained after the initiation of phototherapy were excluded.

TcB sampling was performed with the BiliCheck bilirubinometer (PhilipsRespironics, Koninklijke Philips Electronics NV, Eindhoven, the Netherlands) by properly trained physicians in adequately illuminated rooms and according to the standard described technique. TcB measurements were followed by TSB determinations if the TcB value was ≥15 mg/dL, or if the TcB value exceeded or was closer than 2 mg/dL to the phototherapy hour-specific threshold recommended by the AAP. TSB measurements were performed by direct spectrophotometry (Unistat Bilirubinometer, Richert Inc, Depew, NY).

Risk Factors

Factors known to be associated with the development of significant hyperbilirubinemia were recorded. Demographic and perinatal data were
Mean TcB values and TcB percentiles for each designated time, and the mean TcB increase for 12-hour time intervals up to 96 postnatal hours, were calculated. The effect of different demographic and perinatal factors on the TcB increase was determined and expressed in μg/dL/h. The effect of different demographic and perinatal factors on the TcB increase was assessed for each time epoch by multiple regression analysis. TcB percentile curves were created and selected percentile curves were plotted for comparison on an hour-specific TcB nomogram, which reflects the natural course of TcB levels in white, healthy, term, and near-term neonates, and on the Bhutani predictive nomogram. The data were analyzed by using SPSS version 17.0 (SPSS, Inc, Chicago, IL).

RESULTS

During the study period, 7302 neonates were cared for in our well-infant nursery; of these, 450 (6.2%) developed significant hyperbilirubinemia. Thirty-one infants were excluded from the study (24 owing to significant hyperbilirubinemia within the first 24 hours and 7 owing to the inconvenient timing of TcB measurements), resulting in a final sample of 419 neonates from whom a total of 2454 TcB measurements were recorded and analyzed. Fifty neonates (11.9%) reached phototherapy thresholds between 24 and 48 hours, 145 (34.6%) between 48 and 72 hours, 149 (35.6%) between 72 and 96 hours, 47 (11.2%) between 96 and 120 hours, and 28 infants (6.7%) developed significant hyperbilirubinemia after 120 postnatal hours. Eighteen neonates (4.3%) were diagnosed with hyperbilirubinemia within the first 24 hours, 47 (11.2%) between 24 and 36 hours, whereas rhesus incompatibility affected bilirubin increment rate between 24 and 36 hours. A similar relation was noted between percent weight loss and rate of TcB increase in relation to the presence of different risk factors are presented in Appendix 1. Multiple regression analysis revealed that ABO incompatibilities and G6PD deficiency were positively related to the rate of TcB increase during the first 36 and 48 postnatal hours respectively, whereas rhesus incompatibility affected bilirubin increment rate between 24 and 36 hours. The rates of TcB increase after the 48 postnatal hours, whereas the effect of breastfeeding became significant after the age of

Statistics

Mean TcB values and TcB percentiles for each designated time are presented in Table 2. The mean TcB increase for different 12-hour time epochs are presented in Table 3, whereas the rates of TcB increase were calculated. The rates of TcB increase for the different 12-hour time intervals up to 96 postnatal hours were calculated. The rate of TcB increase was determined and expressed in μg/dL/h. The effect of different demographic and perinatal factors on the TcB increase was assessed for each time epoch by multiple regression analysis. TcB percentile curves were created and selected percentile curves were plotted for comparison on an hour-specific TcB nomogram, which reflects the natural course of TcB levels in white, healthy, term, and near-term neonates, and on the Bhutani predictive nomogram.
Mean TcB Increment Rates and the Effect of Different Factors on the Rate of TcB Increase

**TABLE 3**

<table>
<thead>
<tr>
<th>Time Intervals, h</th>
<th>Mean Increment Rate (SD), mg/dL/h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male Gender</td>
</tr>
<tr>
<td>0</td>
<td>0.039</td>
</tr>
<tr>
<td>12</td>
<td>0.086</td>
</tr>
<tr>
<td>24</td>
<td>0.107</td>
</tr>
<tr>
<td>36</td>
<td>0.221*</td>
</tr>
<tr>
<td>48</td>
<td>0.204*</td>
</tr>
<tr>
<td>60</td>
<td>0.204*</td>
</tr>
</tbody>
</table>

The current study is the first to focus on the natural history of TcB levels before the development of significant hyperbilirubinemia in neonates. In 2 previous population-based reports, we have shown that term and late preterm neonates who required phototherapy presented a quite different pattern of TcB increase compared with their counterparts who did not develop significant jaundice. After an initial (up to 24–36 postnatal hours) TcB increase, which was comparable between the 2 groups, the rate of increase remained high in neonates who required phototherapy, whereas it decreased in those who did not develop significant hyperbilirubinemia. An important overlap of TcB values between the 2 groups was also reported. The results of the current study corroborate these earlier findings, suggesting that the use of such population-based nomograms for predicting subsequent significant hyperbilirubinemia in neonates should be done with extreme caution, especially during the first 24 to 48 postnatal hours.

In the current study, we assessed the effect of such factors in neonates with high TSB levels (17–22.9 mg/dL at age ≥48 hours), and they found that smaller gestational age, breastfeeding, and exclusive breastfeeding were important predictors for severe hyperbilirubinemia. Although this study cannot be compared with ours because of major methodological differences, it revealed that risk factors known to be associated with significant hyperbilirubinemia in the general population may also be applicable in neonates with already increased bilirubin levels. In the current study, neonates with smaller gestational age, ABO incompatibility, Rh incompatibility, increased weight loss, and exclusive breastfeeding had higher rates of TcB increase. Interestingly, the effect of these factors was time dependent. Blood incompatibilities and G6PD deficiency affected the rate of TcB increase earlier (ie, during the first 36–48 hours), whereas smaller gestational age, increased weight loss, and exclusive breastfeeding had a later effect. These findings, which are in...
accordance with the results of earlier reports,20–23 may assist health care professionals in stratifying the risk for extreme hyperbilirubinemia and planning appropriate follow-up strategies for neonates with borderline bilirubin levels.

Although the current study was not designed to assess the reliability of predictive nomograms in identifying neonates at risk for significant hyperbilirubinemia, important findings emerged when TcB values of our cohort were plotted on the nomogram developed by Bhutani et al.18 This nomogram is a popular predictive tool that has been broadly recommended for predischarge risk assessment of subsequent severe hyperbilirubinemia.24 Although the Bhutani nomogram was based on, and designated for, TSB measurements, the demarcator between its high- and low-intermediate risk zone (ie, the 75th-percentile curve of the nomogram) has been proposed as a reasonable cutoff for identifying high-risk TcB values.16 Moreover, a different approach is recommended for high-intermediate risk compared with low-intermediate risk TcB measurements.24 The results of the current study, however, suggest that the 75th-percentile curve of the Bhutani nomogram could not be used as a reliable high-risk cutoff in our population, as ~10% of the TcB measurements were within the low-intermediate risk zone during the first 60 postnatal hours, and thus would be misclassified as low risk (Fig 2). Our findings corroborate previous concerns regarding false-negative rates of the Bhutani predictive nomogram,25 especially when TcB measurements are used.26,27

The findings of the current study should be considered in the context of its potential limitations. We provide data obtained from a sample of white Greek neonates and from a single center. Therefore, although new-generation transcutaneous bilirubinometers have been shown not to be affected by skin pigmentation and proved highly effective among heterogeneous populations,16,28 our findings may not be generalizable beyond our settings. The gold standard used to define significant hyperbilirubinemia in this study was the AAP phototherapy thresholds,2 an approach that might be considered questionable.14 However, there is evidence that the implementation of the AAP guidelines for the management of neonatal jaundice was associated with a dramatic decline in the incidence of severe and dangerous hyperbilirubinemia.3,4 We consider, therefore, that this “therapeutic”14 definition of significant hyperbilirubinemia is a realistic, safe, and closer to clinical practice approach.

CONCLUSIONS

The current study provides data on the natural course of TcB levels before the development of significant

FIGURE 1
Graphical comparison between the 5th-, 10th-, and 50th-percentile TcB curves of our study population and the 95th-, 75th-, and 50th-percentile curves of an hour-specific TcB nomogram11 that reflects the natural course of TcB levels in white, healthy, term, and near-term neonates. *Percentile curves of the TcB nomogram.11

FIGURE 2
Graphical comparison between the 5th- and 10th-percentile TcB curves of our study population and Bhutani’s predictive nomogram. HRZ, high-risk zone; HIRZ, high-intermediate risk zone; LIRZ, low-intermediate risk zone; LRZ, low-risk zone; TcB, transcutaneous bilirubin.
hyperbilirubinemia in a white population of term and near-term neonates. Infants with smaller gestational age, blood incompatibilities, G6PD deficiency, increased weight loss, and who were exclusively breastfed, presented higher rates of TcB increase; the effect of these factors, however, was time dependent. These findings may assist health care professionals involved in neonatal care in assessing the risk for significant hyperbilirubinemia and planning appropriate follow-up strategies for neonates with borderline bilirubin levels.

REFERENCES

## APPENDIX 1 Mean Rates of TcB Increase at Different Time Intervals in Relation to Various Risk Factors for Significant Hyperbilirubinemia

<table>
<thead>
<tr>
<th>Time Intervals, h (No. of Paired Measurements)</th>
<th>Gender, males/females</th>
<th>Prematurity, yes/no</th>
<th>Delivery, vaginal/cesarean</th>
<th>Feeding, breast/formula(^d)</th>
<th>Weight loss, yes/no(^e)</th>
<th>ABO incompatibility, yes/no</th>
<th>Rhesus incompatibility, yes/no</th>
<th>Group, positive/ negative</th>
<th>G6PD deficiency, yes/no</th>
<th>Bruising or cephalhematoma, yes/no</th>
<th>Previous sibling with jaundice, yes/no</th>
</tr>
</thead>
<tbody>
<tr>
<td>12–24 (298)</td>
<td>0.25 / 0.22(^a)</td>
<td>0.24 / 0.23</td>
<td>0.24 / 0.22*</td>
<td>0.24 / 0.23*</td>
<td>0.24 / 0.23*</td>
<td>0.29 / 0.23*</td>
<td>0.27 / 0.23*</td>
<td>0.28 / 0.23*</td>
<td>0.29 / 0.22*</td>
<td>0.23 / 0.23</td>
<td>0.22 / 0.23</td>
</tr>
<tr>
<td>24–36 (364)</td>
<td>0.23 / 0.21</td>
<td>0.22 / 0.21</td>
<td>0.24 / 0.21*</td>
<td>0.22 / 0.21*</td>
<td>0.24 / 0.21*</td>
<td>0.26 / 0.21*</td>
<td>0.26 / 0.21*</td>
<td>0.25 / 0.21*</td>
<td>0.28 / 022*</td>
<td>0.22 / 0.21</td>
<td>0.22 / 0.21</td>
</tr>
<tr>
<td>36–48 (326)</td>
<td>0.21 / 0.20</td>
<td>0.21 / 0.21</td>
<td>0.21 / 0.20*</td>
<td>0.22 / 0.18*</td>
<td>0.21 / 0.21*</td>
<td>0.24 / 0.21*</td>
<td>0.24 / 0.21*</td>
<td>0.23 / 0.21*</td>
<td>0.27 / 0.21*</td>
<td>0.21 / 0.21</td>
<td>0.21 / 0.21</td>
</tr>
<tr>
<td>48–60 (229)</td>
<td>0.19 / 0.19</td>
<td>0.19 / 0.19</td>
<td>0.19 / 0.19</td>
<td>0.22 / 0.18*</td>
<td>0.19 / 0.19</td>
<td>0.21 / 0.19</td>
<td>0.19 / 0.19</td>
<td>0.20 / 0.19*</td>
<td>0.25 / 0.19</td>
<td>0.20 / 0.19</td>
<td>0.20 / 0.19</td>
</tr>
<tr>
<td>60–72 (195)</td>
<td>0.19 / 0.19</td>
<td>0.19 / 0.19</td>
<td>0.18 / 0.19</td>
<td>0.23 / 0.18*</td>
<td>0.18 / 0.19</td>
<td>0.21 / 0.19</td>
<td>0.19 / 0.19</td>
<td>0.20 / 0.19*</td>
<td>0.25 / 0.19</td>
<td>0.19 / 0.19</td>
<td>0.19 / 0.19</td>
</tr>
<tr>
<td>72–84 (118)</td>
<td>0.11 / 0.10</td>
<td>0.10 / 0.10</td>
<td>0.10 / 0.10</td>
<td>0.14 / 0.09*</td>
<td>0.08 / 0.09</td>
<td>0.13 / 0.09*</td>
<td>0.09 / 0.09</td>
<td>0.12 / 0.09*</td>
<td>0.15 / 0.09*</td>
<td>0.10 / 0.09</td>
<td>0.10 / 0.09</td>
</tr>
<tr>
<td>84–96 (75)</td>
<td>0.08 / 0.09</td>
<td>0.08 / 0.09</td>
<td>0.08 / 0.09</td>
<td>0.13 / 0.09*</td>
<td>0.12 / 0.09*</td>
<td>0.13 / 0.09*</td>
<td>0.10 / 0.09</td>
<td>0.11 / 0.09*</td>
<td>0.13 / 0.09*</td>
<td>0.10 / 0.09</td>
<td>0.10 / 0.09</td>
</tr>
</tbody>
</table>

Data are rates of TcB increase in mg/dL/h. Significant values are indicated with an asterisk. NA, non applicable.

\(^a\) \(P < .05\).
\(^b\) \(P < .01\).
\(^c\) \(P < .001\).
\(^d\) Breastfeeding versus formula or mixed feeding.
\(^e\) Weight loss > 3.3% per 24 h (75th percentile of the study population).
\(^f\) Insufficient number of neonates with the risk factor present.
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