Effect of Phototherapy on the Reliability of Transcutaneous Bilirubin Devices in Term and Near-Term Infants: A Systematic Review and Meta-Analysis

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Key Words
Transcutaneous bilirubin · Correlation coefficient · Bland-Altman difference plots · Systematic review · Meta-analysis

Abstract
Background: Transcutaneous bilirubin (TcB) devices are commonly used for screening of hyperbilirubinemia in term and near-term infants not exposed to phototherapy. However, the accuracy of TcB devices in infants exposed to phototherapy is unclear. Objectives: To conduct a systematic review of studies comparing TcB devices with total serum bilirubin (TSB) in infants receiving phototherapy or in the postphototherapy phase. Methods: MEDLINE, EMBASE, Cochrane Library, CINAHL and Scopus databases (from inception to May 8, 2014) were searched. Additional citations were identified from the bibliography of selected articles and from the abstracts of conference proceedings. The studies were included if they compared TcB results with TSB in infants receiving phototherapy or in the postphototherapy phase. The pooled estimates of correlation coefficients (r) during phototherapy were: covered sites 0.71 (95% CI 0.64–0.77, 11 studies), uncovered sites 0.65 (95% CI 0.55–0.74, 8 studies), forehead 0.70 (95% CI 0.64–0.75, 12 studies) and sternum 0.64 (95% CI 0.43–0.77, 5 studies). Two studies also provided results as Bland-Altman difference plots (mean TcB-BSB differences –29.2 and 30 μmol/l, respectively). The correlation coefficient improved marginally in the postphototherapy phase (r = 0.72, 95% CI 0.64–0.78, 4 studies).

Conclusion: We found a moderate correlation between TcB and TSB during phototherapy with a marginal improvement in the postphototherapy phase. Further research is needed before the use of TcB devices can be recommended for these settings.

Introduction

Jaundice is common in the newborn period with the majority of neonates developing visible jaundice within the first week of life [1, 2]. Although in a significant majority this does not possess any risk to the newborn, up to 10% of term and 25% of near-term neonates develop sig-
significant hyperbilirubinemia necessitating phototherapy [3]. Newborn jaundice is known to have cephalocaudal progression [4]; however, visual assessment of serum bilirubin has been shown to correlate poorly with measured bilirubin levels in recent studies [2, 5, 6]. Blood sampling for the estimation of serum bilirubin is one of the commonest tests ordered in the neonatal units. This is often done by heel prick and is considered painful, with potential long-term consequences [7].

Transcutaneous bilirubin (TcB) devices estimate serum bilirubin noninvasively from the skin [8]. These devices have been shown to correlate well with serum bilirubin levels in term and preterm infants prior to the start of phototherapy [9–14]. The American Academy of Pediatrics recommends the use of TcB devices for the screening of jaundice in infants at more than 35 weeks of gestation [15].

Infants requiring phototherapy need frequent measurement of serum bilirubin to assess the response to treatment. However, the role of TcB devices during phototherapy or in the postphototherapy phase is not clear. Recently there has been an increasing trend towards home phototherapy in the low-risk term and near-term infants [16–19], where arranging follow-up assessments of serum bilirubin is cumbersome. Such infants could also benefit from assessment by a TcB device, if validated.

The objective of this systematic review was to assess the diagnostic accuracy of transcutaneous devices as compared to the total serum bilirubin (TSB) measurement in term and near-term infants receiving phototherapy during the neonatal period.

Methods

Search and Selection

Several databases including MEDLINE, EMBASE, Cochrane Library, CINAHL and Scopus were systematically searched (initially searched in August 2013 and search updated on May 8, 2014). Both controlled vocabulary terms (e.g. MeSH, EMTREE, etc.) and key words were used to search the concepts: neonatal, bilirubinometers, transcutaneous, total serum bilirubin and phototherapy. Additional terminology and predefined database limits were added to restrict the references to those related to less than 1 month of age. No language restriction was applied (refer to the Appendix for the detailed search strategy). Conference proceedings and bibliography of included studies were also searched for any potential studies.

Studies were included in the review if they enrolled infants ≥34 weeks of gestational age and compared TcB results to TSB estimation during the neonatal period while receiving phototherapy. We excluded pilot studies (defined a priori as those enrolling ≤20 subjects) and studies enrolling infants of all gestational ages but not providing separate data for the population of interest. The outcome of interest was agreement statistic between TcB and TSB measurements provided either as correlation coefficient or as the mean and standard deviations of absolute differences in bilirubin values by the two methods (Bland-Altman difference plots) [20].

Data Extraction and Assessment of Risk of Bias

Titles, abstracts and citations were independently assessed by two reviewers for inclusion based on predefined selection criteria. Data from included studies were extracted on a specifically designed data extraction form by one reviewer and checked for accuracy by a second reviewer. Risk of bias assessments were conducted according to the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool [21]. This tool consists of 4 key domains: patient selection, index test, reference standard and flow and timing. Each study is assessed for risk of bias in each of the domains and for concerns regarding applicability in the first 3 domains. Disagreements were resolved by consensus among the members of the review team.

Data Analysis

We meta-analyzed the available data both from the correlation coefficients of the measurements of TcB and TSB, and from the Bland-Altman difference plots. All correlations were first converted to Fisher Z scores prior to being pooled. The resulting pooled Fisher Z scores were then transformed back into standard correlation coefficients for the ease of interpretation. For Bland-Altman difference plots, we pooled the mean TcB-TSB differences and variance across eligible studies for estimation of bias and standard deviation, respectively, by methods as described by Peyton and Chong [22].

A priori subgroup analyses were planned to explore the influence of the shielded area, site of TcB measurement and the type of TcB device used. We also assessed the accuracy of the TcB devices in the postphototherapy phase where studies provided those data.

Meta-analyses were performed using Review Manager version 5.2 software (Nordic Cochrane Centre, Cochrane Collaboration, 2011, Copenhagen, Denmark). The I² statistic was calculated for each analysis to quantify heterogeneity across studies. Forest plots were created using SPlus Software version 3.4 (TIBCO Software Inc., 2010).

Results

We identified 14 studies [17, 23–35] providing 2,082 paired measurements of TcB and TSB in 1,319 patients who fulfilled the inclusion criteria (fig. 1). The baseline characteristics of the included studies are presented in table 1. Studies varied in terms of: whether the site(s) of measurement were shielded from phototherapy; the actual site of TcB measurement (forehead = 12 studies; sternum = 5 studies and other sites = 2 studies); the TcB device used (Bilicheck = 1 study; JM 103 = 3 studies; JM 101 = 10 studies); the method used for serum bilirubin measurement (direct spectrophotometry only = 7 studies; diazo method only = 5 studies; both = 1 study, and meth-
Results for risk of bias assessments for the included studies are provided in table 2. The majority of the included studies were assessed as low risk for bias with respect to patient selection, index test, reference standard and flow timing. However, there were some applicability concerns with most of the included studies. Ten studies [24–33] employed TcB devices (Minolta Airshields Jaune-dice/Bilirubin Meter, i.e. JM 101) that are no longer used in clinical practice. In the study by Rylance et al. [23], although the blood for estimation of TSB was collected at the time of TcB estimation, samples were processed once a day resulting in greater time lag and thus risk of degradation of bilirubin from light and heat [36]. Nine studies [17, 23, 25, 26, 29, 30, 32, 33, 35] conducted the TcB and TSB estimations simultaneously or within 30 min, whereas the remaining 5 [24, 27, 28, 31, 34] did not specify the time difference between the two tests.

Results of Meta-Analyses of Data from Subjects during Phototherapy (13 Studies)
Correlation Coefficients
All studies provided results for correlation coefficients. Separate meta-analyses were conducted for whether the site of measurement was shielded from direct phototherapy light (covered and uncovered areas; fig. 2) and for the two commonly used sites of measurement, i.e. the forehead and sternum (fig. 3).

The pooled estimate of the correlation coefficients from the 11 studies [23–30, 32, 33, 35] providing data from sites covered during phototherapy was 0.71 (95% CI 0.64–0.77). The estimate from the uncovered sites was slightly lower (r = 0.65, 95% CI 0.55–0.74, in 8 studies) [17, 24, 26, 27, 29–32]; however, this difference was not statistically significant (fig. 2). Similarly, there was no statistically significant difference noted between the estimates from the newer TcB devices (JM 103 and Bilicheck) as compared to the older devices.

Results of the Pooled Estimates according to the Site of Measurement. Twelve studies provided data for the TcB measurements at the forehead site for comparison with TSB results, and the summated correlation coefficient from this site was 0.70 (95% CI 0.64–0.75). The majority of the included studies covered the forehead site; however, 2 studies [29, 32] also provided data from an uncovered area over the forehead. The summated correlation coefficient was unchanged after removing those data (r = 0.70, 95% CI 0.64–0.76). The pooled estimate from the studies providing data for TcB measurements at the sternum (5 studies) was 0.64 (95% CI 0.43–0.77). There was significant heterogeneity noted in this estimate ($I^2 = 77\%$).
Bland-Altman Difference Plots

Only 2 studies [17, 23] provided data for Bland-Altman difference plots. The study by Reyes et al. [17] using the Bilicheck device at the forehead site showed that TcB underestimated TSB by a mean difference of 29.2 μmol/l. On the other hand, the study by Rylance et al. [23] using the JM 103 device showed that TcB overestimated TSB (mean difference = 30 μmol/l, 95% precision limits ±79 μmol/l).

TcB-TSB Comparison in Postphototherapy Phase

(4 Studies)

Four of the included studies [27, 32, 34, 35] also provided data for infants in the postphototherapy phase (fig. 4). The correlation between TcB and TSB readings improved marginally following discontinuation of phototherapy (r = 0.72, 95% CI 0.64–0.78). Tan and Dong [32] noted further improvement in the correlation coef-
Table 2. Risk of bias assessments of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk of bias</th>
<th>Applicability concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>patient</td>
<td>index test</td>
</tr>
<tr>
<td>Juster-Reicher [34], 2015</td>
<td>✓ ✓ ✓</td>
<td></td>
</tr>
<tr>
<td>Rylance [23], 2014</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓</td>
</tr>
<tr>
<td>Panburana [35], 2010</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓</td>
</tr>
<tr>
<td>Reyes [17], 2008</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓</td>
</tr>
<tr>
<td>Felc [25], 2005</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓</td>
</tr>
<tr>
<td>Mahajan [30], 2005</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓</td>
</tr>
<tr>
<td>Tan [32], 2003</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓</td>
</tr>
<tr>
<td>Kumar [29], 1994</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓</td>
</tr>
<tr>
<td>Dominguez [24], 1993</td>
<td>✓ ✓ ✓</td>
<td></td>
</tr>
<tr>
<td>Rey Galan [31], 1992</td>
<td>✓ ✓ ✓</td>
<td></td>
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<tr>
<td>Fok [26], 1986</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓</td>
</tr>
<tr>
<td>Galletto [27], 1983</td>
<td>?</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td>Vaisman [33], 1983</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓</td>
</tr>
<tr>
<td>Hannemann [28], 1982</td>
<td>✓ ✓ ✓</td>
<td></td>
</tr>
</tbody>
</table>

✓ = Low risk; ? = unclear risk.

Fig. 2. Pooled estimates of correlation coefficients at covered and uncovered sites during phototherapy. C = TcB data from ‘covered’ area over forehead; UC = TcB data from ‘uncovered’ area over forehead; SFD = small-for-dates subset; AFD = appropriate-for-dates subset.
coefficients on the second day after phototherapy as compared to the first reading taken 18–24 h after discontinuation of phototherapy (sternum: $r = 0.84$ on day 2 vs. 0.80 for day 1; forehead: $r = 0.80$ on day 2 vs. 0.70 for day 1).

### Discussion

We identified 14 studies evaluating the diagnostic accuracy of various TcB devices in term and near-term infants after the onset of phototherapy. The results of this review show a moderate correlation [37] between the TcB...
and the TSB estimation in infants while receiving phototherapy, with a slightly better correlation noted at the forehead site or when the site of measurement was shielded from phototherapy light. The limited data available from the 4 studies assessing agreement between TcB and TSB estimation following discontinuation of phototherapy indicate a somewhat better agreement in the post-phototherapy phase.

Whilst all studies provided correlation coefficients, only 2 studies provided data for the Bland-Altman difference plots. Unfortunately, the translation into clinical practice of a moderate correlation coefficient noted between TcB and TSB tests is difficult, as it does not provide information in terms of the expected difference between these measurements for an individual patient. On the other hand, data presented as Bland-Altman difference plots (in terms of bias and precision estimates) could allow a reasonable prediction of the range of the TSB values likely for a given TcB reading, which is thus much more helpful for clinical decision-making [20]. The limited data from the 2 studies providing Bland-Altman difference plots prevents us from making any firm recommendations for practice.

The pooled estimates of correlation coefficients noted here are much weaker than the estimates noted in several studies of term and near-term infants prior to subjects receiving phototherapy [9–13], where the correlation was noted to be high (i.e. coefficients typically ranged between 0.85 and 0.94) and the use of the TcB devices is recommended for decreasing blood sampling during screening for neonatal jaundice [15, 38, 39]. Based on the data presented here, the TcB devices cannot be relied upon for assessment of bilirubin in infants exposed to phototherapy. However, the improvement in TcB-TSB agreement noted in the postphototherapy phase seems to indicate that in future studies the accuracy of the TcB devices should be separately assessed in the period following discontinuation of phototherapy. Furthermore, the temporal changes in TcB-TSB agreement in the postphototherapy phase should also be studied, as suggested in one study [32].

Our review has a few limitations. First, the majority of the studies were done using older versions of TcB devices which are no longer in practice. It is possible that the current version of these devices may have better agreement with TSB. Also, one of the studies that assessed a TcB device used currently in practice [23] could be biased as blood samples for TSB estimation were stored for several hours before processing (processed once a day) leading to a significant risk of bilirubin degradation due to environmental factors. Second, we decided a priori to exclude studies enrolling <20 participants, as data from smaller studies are known to often distort results of the meta-analyses due to many reasons [40]. Third, the majority of the included studies presented results as correlation coefficients which are difficult to translate into clinical practice as discussed above. Fourth, we could not apply a formal test to check for publication bias due to a limited number of studies; however, the funnel plot of the included studies did not reveal any obvious asymmetry. Lastly, several of the studies included in the meta-analysis provided multiple readings from each patient enrolled, leading to the statistical risks of dependency of data. However, the results from the studies providing one reading per patient enrolled were not significantly different from those providing multiple data points per patient.

**Conclusion**

The results of this systematic review show that the TcB devices are much less accurate in estimating serum bilirubin values in infants when receiving phototherapy as compared to their documented accuracy in the prephototherapy period. The limited data available from the studies assessing agreement between TcB and TSB tests following discontinuation of phototherapy show a somewhat improved accuracy of the TcB devices in the postphototherapy phase. Further research with currently available TcB devices is needed before their use of TcB devices can be recommended in any of the settings that were the subject of this review.

**Acknowledgment**

We are grateful to Dr. Pharuhad Pongmee for his assistance with the identification of eligible studies for this systematic review.

**Disclosure Statement**

The authors do not have any financial disclosure to make.
Appendix

Bilirubinometers and Phototherapy Strategy

Database: Ovid MEDLINE® In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® <1946 to present>

Search Strategy:

1. phototherapy.mp or exp Phototherapy/ (29,242)
2. (light adj2 therap*).mp [mp = title, abstract, original title, name of substance word, subject heading word, key word heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1,668)
3. phototherapies.mp (68)
4. photoradiation therap*.mp [mp = title, abstract, original title, name of substance word, subject heading word, key word heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (173)
5. 1 or 2 or 3 or 4 (29,965)
6. (transcutaneous* and (bilirubin* or hyperbilirubin* or jaundice*)).mp [mp = title, abstract, original title, name of substance word, subject heading word, key word heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (372)
7. tcb.mp [mp = title, abstract, original title, name of substance word, subject heading word, key word heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (759)
8. (bilirubinometer* or biliblitz* or bilitest* or bilichek* or bilichek* or tcbr or icterometer*).mp [mp = title, abstract, original title, name of substance word, subject heading word, key word heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (178)
9. 6 or 7 or 8 (1,066)
10. 5 and 9 (126)

Database: EMBASE <1974 to 2013 week 33>

Search Strategy:

1. phototherapy.mp or exp Phototherapy/ (52,640)
2. (light adj2 therap*).mp [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, key word] (2,478)
3. phototherapies.mp (96)
4. photoradiation therap*.mp [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, key word] (198)
5. 1 or 2 or 3 or 4 (53,514)
6. (transcutaneous* and (bilirubin* or hyperbilirubin* or jaundice*)).mp [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, key word] (502)
7. tcb.mp [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, key word] (940)
8. (bilirubinometer* or biliblitz* or bilitest* or bilichek* or bilichek* or tcbr or icterometer*).mp [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, key word] (231)
9. 6 or 7 or 8 (1,349)
10. 5 and 9 (174)

Ovid Technologies Inc. E-Mail Service

Search for: 5 and 9
Results: 1

Search Strategy:

1. phototherapy.mp or exp Phototherapy/ (2,426)
2. (light adj2 therap*).mp [mp = ti, ab, kw, ct, ot, sh, hw] (452)
3. phototherapies.mp (19)
4. photoradiation therap*.mp [mp = ti, ab, tx, kw, ct, ot, sh, hw] (4)
5. 1 or 2 or 3 or 4 (2,631)
6. (transcutaneous* and (bilirubin* or hyperbilirubin* or jaundice*)).mp [mp = ti, ab, tx, kw, ct, ot, sh, hw] (30)
7. tcb.mp [mp = ti, ab, tx, kw, ct, ot, sh, hw] (11)
8. (bilirubinometer* or biliblitz* or bilitest* or bilicheck* or bilichek* or tcbr or icterometer*).mp [mp = ti, ab, tx, kw, ct, ot, sh, hw] (12)
9. 6 or 7 or 8 (40)
10. 5 and 9 (15)

1. phototherapy.mp or exp Phototherapy/ (2,426)
2. (light adj2 therap*).mp [mp = ti, ab, kw, ct, ot, sh, hw] (452)
3. phototherapies.mp (19)
4. photoradiation therap*.mp [mp = ti, ab, tx, kw, ct, ot, sh, hw] (4)
5. 1 or 2 or 3 or 4 (2,631)
6. (transcutaneous* and (bilirubin* or hyperbilirubin* or jaundice*)).mp [mp = ti, ab, tx, kw, ct, ot, sh, hw] (30)
7. tcb.mp [mp = ti, ab, tx, kw, ct, ot, sh, hw] (11)
8. (bilirubinometer* or biliblitz* or bilitest* or bilicheck* or bilichek* or tcbr or icterometer*).mp [mp = ti, ab, tx, kw, ct, ot, sh, hw] (12)
9. 6 or 7 or 8 (40)
10. 5 and 9 (15)

Scopus

(TITLE-ABS-KEY(bilirubinometer* OR biliblitz* OR bilitest* OR bilicheck* OR bilichek* OR tcbr OR icterometer*)) AND (TITLE-ABS-KEY(transcutaneous* W/7 (bilirubin* OR hyperbilirubin* OR jaundice*)))

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all(bilirubinometer* OR biliblitz* OR bilitest* OR bilicheck* OR bilichek* OR tcbr OR icterometer*) OR all(transcutaneous* NEAR/2 (bilirubin* OR hyperbilirubin* OR jaundice*)) AND all(photo therap* OR phototherap* OR light therap* OR light treatment* OR photoradiat*)

COMPEXDEX and INSPEC searched together August 23, 2013

((photo NEAR/1 therap* OR phototherap OR light NEAR/1 therap* OR light NEAR/1 treatment* OR photoradiat*) AND (1985–2013 WN YR)) and (((bilirubinometer* OR biliblitz* OR bilitest* OR bilicheck* OR bilichek* OR tcbr OR icterometer*) AND (1985–2013 WN YR)) OR ((transcutaneous* NEAR/2 bilirubin* OR transcutaneous* NEAR/2 hyperbilirubin* OR transcutaneous* NEAR/2 jaundice*)) AND (1985–2013 WN YR)))

Search Updated May 8, 2014. All databases plus PubMed 38 record from 2013 to current.
References


