A Prospective Comparison of Transcutaneous and Serum Bilirubin Within Brief Time Intervals

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Abstract
The American Academy of Pediatrics recommends screening newborns ≥35 weeks’ gestation with total serum bilirubin (TSB) or transcutaneous bilirubin (TcB) to detect hyperbilirubinemia. Retrospective studies show TcB measurements strongly correlate with TSB; however, few prospective trials document this relationship. Furthermore, Dräger’s newest TcB instrument, JM-105, remains unstudied in the United States. We measure TcB on foreheads and sternums of newborns using JM-105 and Bilichek devices within 30 minutes of TSB measurement. We find best overall TcB/TSB correlation with JM-105 on the sternum (mean TcB-TSB difference: −0.21 ± 1.15 mg/dL). Correlations between paired measurements for TcB on the sternum using JM-105 were 0.93 for all TSB levels (n = 178), 0.82 for TSB > 10 (n = 19), 0.69 for TSB > 12 (n = 11), and 0.52 for TSB > 15 (n = 6). TcB accuracy via JM-105 on the sternum significantly differed among races (P < .001). For 5% of paired measurements, TcB with JM-105 on the sternum underestimated TSB by ≥2 mg/dL, and for <1% by ≥3 mg/dL.

Keywords
transcutaneous bilirubin screening, hyperbilirubinemia, jaundice, Dräger JM-105, Bilichek

Introduction
The American Academy of Pediatrics recommends screening newborns 35 or more weeks of gestation for either a total serum bilirubin (TSB) or a transcutaneous bilirubin (TcB) measurement in order to detect and subsequently treat significant hyperbilirubinemia.¹ While hyperbilirubinemia (jaundice) is a very common and most often harmless condition in neonates (clinically evident in over 80% of newborns during the first week of life²), excessive hyperbilirubinemia can lead to bilirubin encephalopathy (kernicterus) causing irreversible brain damage.³ Although TSB measurement via heel stick blood sampling is the most accurate way to determine the true serum bilirubin level, heel sticks are painful, stressful for the parents, time-consuming, and can lead to long-term consequences such as osteomyelitis, skin infections at the site of sampling, and calcium deposition at the heel-stick site.⁴⁻⁷

Multiple investigators have found that TcB measurements correlate well with TSB levels.⁸⁻¹⁴ Taylor et al looked retrospectively at 925 matched measurements of TcB (measured on various sites of newborns and with various instruments) and TSB measured within 2 hours of each other and found that the correlation between them was 0.78.⁵ Previously, a correlation as high as 0.96 was reported by Grohmann et al for the JM-102, JM-103, and Bilichek devices when looking prospectively at 122 white infants.¹¹ While the newest transcutaneous meter from Dräger, the JM-105, has never been studied in the United States,¹⁵ Maisels et al and Romagnoli et al both found that its predecessor, the JM-103, was easier and more practical to use compared to the Bilichek meter despite their similar performances.

Despite multiple studies showing strong correlation between TcB devices and TSB, newborn nursery physicians and pediatricians in outpatient clinics use various
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and subjective thresholds to determine when to obtain a TSB on their patients. Our study prospectively compares the JM-105 with the Bilichek meter to determine their correlations with TSB in patients in our newborn nursery and in the outpatient setting at our pediatric clinic in hopes of providing a more standard threshold of when to rely on a TcB and when it is necessary to utilize a TSB.

Patients and Methods

Potential study participants were recruited in the University of North Carolina Women’s Hospital newborn nursery and in the pediatric primary care outpatient clinic from June to August 2015. Inclusion criteria included infants with gestational age ≥35 weeks, no history of phototherapy treatment previously received, and who had not yet had their newborn metabolic screens or who had an ordered TSB by their provider that had not yet been collected. Exclusion criteria included gestational age <35 weeks, age greater than 30 days, other than English- or Spanish-speaking parents, health conditions precluding participation (eg, admission to the neonatal intensive care unit), incarceration or developmental impairment of the mother, or previous phototherapy treatment.

If the infant met study criteria, a research assistant approached the infant’s parents and offered the opportunity to participate in the study. If they agreed, informed consent was obtained and the patient was enrolled. The research assistant then measured the enrolled infant’s TcB on the forehead and sternum using both the JM-105 and Bilichek devices (4 total measurements). These measurements were performed within 30 minutes of the infant having blood drawn for TSB. Blood was expressed from the same heel stick already received for routine newborn screens (~200 µL of extra blood), or was drawn separately if the medical provider had ordered a TSB for other reasons per their discretion. This prevented any unnecessary needle sticks in our participants.

Data were analyzed using Pearson correlations (2-tailed), ANOVA Tukey’s HSD test, and simple correlations using STATA.

Results

A total of 232 patients were approached, 206 patients were consented, and 176 patients met criteria for analysis providing 178 separate TSB/TcB data points for comparison (Figure 1). Table 1 demonstrates the demographics of the patients included in analysis. Overall, TcB measured by the JM-105 on the sternum correlated best with TSB \( r = 0.93 \), followed by JM-105 on the forehead \( r = 0.92 \), Bilichek on the sternum \( r = 0.90 \), and Bilichek on the forehead \( r = 0.89 \); Figure 2).

The mean TcB-TSB difference for JM-105 on the sternum was \(-0.21 \pm 1.15 \text{ mg/dL}\), for JM-105 on the forehead \(0.22 \pm 1.19 \text{ mg/dL}\), for Bilichek on the sternum \(0.85 \pm 1.33 \text{ mg/dL}\), and for Bilichek on the forehead \(0.76 \pm 1.38 \text{ mg/dL}\) (Figure 3).

The correlation between paired (TcB and TSB) measurements using the JM-105 on the sternum was 0.82 for TSB > 10 (n = 19), 0.69 for TSB > 12 (n = 11), and 0.52 for TSB > 15 (n = 6).
Using a TcB cutoff value of 7.0 mg/dL to perform a reflex TSB on 1-day-old infants (our nursery’s current threshold), 28% of infants would have received unnecessary sticks when using the JM-105 on the sternum. This rises to 45% with JM-105 on the forehead, 47% with Bilichek on the forehead, and 52% with Bilichek on the sternum.

TcB accuracy measured by JM-105 on the sternum significantly differed among races (P < .001, ANOVA). The JM-105 overestimated TSB in African Americans by 0.89 mg/dL (95% confidence interval [CI] = 0.38-1.39) on the sternum and by 1.44 mg/dL (95% CI = 0.97-1.92) on the forehead. In Caucasians, the JM-105 underestimated TSB by 0.58 mg/dL (95% CI = 0.37-0.78) on the sternum, but on the forehead the difference was not significant (P = .18). In Hispanic/Latinos, the difference between TSB and TcB was not significant on the sternum (P = .81) but on the forehead it overestimated TSB by 0.54 mg/dL (95% CI = 0.27-0.80).

For 5% of paired measurements, TcB taken by JM-105 on the sternum underestimated TSB by ≥ 2 mg/dL, and for <1% by ≥ 3 mg/dL. There was no significant correlation with age and the TcB-TSB difference when controlling for race and TSB (Figure 4). There was also no significant correlation with TcB-TSB and TSB level as demonstrated in Figure 5 (r = 0.04, P = .58), but there was a significant correlation with the absolute value of the TcB-TSB (r = 0.32, P < .001).

### Discussion

This study found that the Dräger JM-105 most accurately predicted the TSB when used on the mid-sternum when compared to the forehead and to the Bilichek meter on both sites. Based on these results and on results from previous studies that have found the Dräger to be preferable to the Bilichek,[12,16] we recommend that pediatric newborn nurseries and clinics use the Dräger JM-105 when screening infants for TcB. Mishra et al found that screening with a TcB meter lowered the need for blood draws by 34% when compared to a protocol-based visual assessment.[17] This finding was recently supported by a randomized control trial conducted by van den Esker-Jonker et al, in which blood draws were

### Table 1. Demographic and Clinical Characteristics of the 176 Patients Screened.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value, n (%)</th>
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<tbody>
<tr>
<td>Gender, male</td>
<td>74 (42)</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td>36</td>
<td>8 (4.5)</td>
</tr>
<tr>
<td>37</td>
<td>22 (12.5)</td>
</tr>
<tr>
<td>38</td>
<td>25 (14.2)</td>
</tr>
<tr>
<td>39</td>
<td>68 (38.6)</td>
</tr>
<tr>
<td>40</td>
<td>35 (19.9)</td>
</tr>
<tr>
<td>41+</td>
<td>13 (7.4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>27 (15.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>5 (2.8)</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>42 (23.9)</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>White</td>
<td>73 (42.5)</td>
</tr>
<tr>
<td>Multiple races</td>
<td>28 (15.9)</td>
</tr>
</tbody>
</table>

### Figure 2. Correlation of TcB by JM-105 mid-sternum with TSB.

TcB measured by the JM-105 on mid-sternum correlated best overall with TSB (r = 0.93) compared with on the forehead (r = 0.92), or with the Bilichek on sternum (r = 0.90) or forehead (r = 0.89).

### Figure 3. Kernel densities (percentage of results on y-axis, TcB-TSB difference on x-axis).

The mean TcB-TSB differences were -0.21 ± 1.15 mg/dL for JM-105 sternum, 0.22 ± 1.19 mg/dL for JM-105 forehead, 0.85 ± 1.33 mg/dL for Bilichek sternum, and 0.76 ± 1.38 mg/dL.
reduced by 38.5% in the TcB screening group. Thus, although a Dräger JM-105 has a high initial expense (one machine costs approximately $7000 including the equipment to upload the readings directly to an electronic medical record), over time screening for TcB will save money. Maisels and Kring found that the use of TcB meters saves money for newborn nurseries when compared to the cost of TSB measurements. Srinivas et al assessed the cost of a TSB to be approximately $15 per draw (which included the cost of lancets, bullets, heel warmers, nursing time, and laboratory costs). This of course does not take into account nonmonetary costs of the stress of the infants and parents and of the potential complications of heel sticks.

The majority of trials in the United States comparing TSB with TcB were retrospective, and those prospective studies that exist have limited data on the correlation of TcB with higher levels of TSB (>15 mg/dL). This is likely why physicians are nervous to rely solely on TcB when the level is close to an infant’s phototherapy “light level,” or level requiring treatment. Our study found that as the TSB increased, the TcB measurement was less accurate. However unlike previous studies that found that TcB tended to underestimate TSB at higher levels, our study found that TcB both under- and overpredicted TSB equally at higher levels. Additionally, less than 1% of our patients had a greater than 3 mg/dL discrepancy between TSB and TcB. We would therefore encourage physicians screening with TcB to think carefully before ordering a TSB when there is a difference of 3 mg/dL or more between TcB and phototherapy treatment level. For example, if an infant’s TcB is 14 and their phototherapy treatment level by age is 18, they would not necessarily qualify for a TSB. If their phototherapy treatment level was 16, then they would warrant a TSB.

Interestingly, our study also found no correlation between increasing age and TcB-TSB, as has been previously reported by Taylor et al and Yamauchi and Yamanouchi. The significance of this is unclear, but is encouraging for providers in the outpatient setting who frequently screen older infants with TcB meters.

Last, we found that the TSB was significantly overestimated in African Americans, supporting recent findings in black African neonates in Nigeria. We also found a significant underestimation in Caucasians and a significant overestimation in Hispanic/Latinos on the forehead. These are important distinctions for providers to keep in mind when determining whether to order a TSB based on a TcB screen.

Our study had several limitations. First, we did not recruit as many infants with high levels of TSB as we had hoped. So, although we had 19 patients with TSB >10, we only had 4 patients with TSB levels who met criteria for phototherapy. More prospective studies would be helpful to better assess the accuracy of TcB at phototherapy treatment levels (higher TSB levels) in order to better assess whether a threshold of less than 3 mg/dL would be a sufficient screening cutoff for obtaining a TSB. Additionally, even though our recommended method of screening for TcB is by using the Dräger JM-105 on the mid-sternum as it most accurately predicts the TSB, it also tended to slightly underpredict TSB while the Dräger on the forehead and the Bilichek in both sites tended to overpredict. As a screening tool, ideally there would be a slight overprediction to increase sensitivity and decrease false negatives. However, the Dräger on the mid-sternum underpredicted TSB so slightly (mean of 0.21 mg/dL) that we feel it is still the best method to use for screening. Finally, we only recruited 2 patients from our outpatient clinic. Although
we believe our results can be equally applicable to the outpatient setting, it would be beneficial to have more outpatients recruited for a future prospective study using a Dräger JM-105 as outpatients are usually older and therefore often have higher levels of TSB compared to infants in the newborn nursery.

Conclusion
Pediatricians in the newborn nursery and outpatient setting should continue to screen with transcutaneous bilirubins, ideally on the sternum and with the Dräger JM-105. Serum bilirubin should be drawn with discretion, ideally only when the TcB is within 3 mg/dL of the phototherapy treatment threshold for age. This will save practices money, but most importantly decrease stressful, painful, and unnecessary heel sticks in infants.

Author Contributions
DFJ contributed to conception and design, contributed to analysis, and drafted the manuscript. JDK contributed to conception and design, contributed to analysis, EB and LAR contributed to conception and design and analysis. All authors critically revised the manuscript, gave final approval, and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

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