Improving the Management of Hyperbilirubinemia in a Limited-Resource Area

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Chapter 5

Diagnostic Properties of a Portable Point-of-Care Method to Measure Bilirubin and a Transcutaneous Bilirubinometer in Jaundiced Indonesian Newborn Infants

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ABSTRACT

Background: Recently, the Bilistick® 2nd generation a point of care (POC) instrument to measure bilirubin levels has been developed. It is fast and cheaper than transcutaneous bilirubin (TCB) measuring devices, but data on diagnostic properties are scarce.

Objective: To compare performance and accuracy of bilirubin measurements between the second generation of Bilistick® and the JM-105 bilirubinometer.

Method: A prospective study in infants born after ≥ 32 weeks' gestation, and/or a birth weight of ≥ 1500 gram, and a postnatal age ≤14 days in Surabaya, Indonesia. Bilirubin was measured with the Bilistick® 2nd generation (FW 2.0.1), transcutaneous (TCB), and in serum (TSB) with routine laboratory techniques. Mean differences (MD) and 95% limits of agreement (LOA) and correlations were calculated.

Result: We enrolled 149 neonates; 126 had paired measurements of Bilistick® bilirubin, TCB, and TSB. Bilistick® failed in 16 (10.7%) infants. Mean Bilistick® bilirubin-TSB difference was -11 µmol/L (95% LOA -101 to 79 µmol/L) and r=0.738 (p <0.001). Mean TCB-TSB difference was 26 µmol/L (95% LOA -33 to 88) and r=0.785 (p<0.001). The sensitivity, specificity, PPV, and NPV for Bilistick® bilirubin for a TSB above treatment thresholds were 0.74, 0.84, 0.67, and 0.88, respectively, and for TCB 0.92, 0.64, 0.54, and 0.95, respectively.

Conclusion: The Bilistick® 2nd generation underestimates TSB whereas TCB overestimates TSB in jaundiced Indonesian infants. Further improvement of Bilistick®'s diagnostic accuracy with less false-negative readings is essential to increase its use.

Keyword: hyperbilirubinemia, point of care bilirubin, Bilistick® 2nd generation (Firmware 2.0.1), transcutaneous bilirubin

Introduction

Jaundice due to elevated levels of total serum bilirubin (TSB) occurs in up to 80% of all newborn infants in the neonatal period (1). Severe neonatal hyperbilirubinemia (SNH) may lead to acute bilirubin encephalopathy (ABE) or kernicterus spectrum disorder (KSD). ABE, KSD and even bilirubin-associated mortality are commonly reported in low- and middle-income countries (LMICs) where incidence of severe neonatal hyperbilirubinemia (SNH) is higher compared to high income countries (2,3). KSD is preventable when high bilirubin levels are timely treated (2,4). Several methods to detect unconjugated hyperbilirubinemia exist, such as visual assessment with the Kramer score, transcutaneous bilirubinometry (TCB), and measurement of total serum bilirubin (TSB). The Kramer score has been used for decades (5) and many health care professionals still rely on it, despite evidence that visual assessment detects jaundice, but does not reliably differentiate between harmless TSB levels and those requiring treatment (6–8). In contrast, TCB measurements provide fast and reliable estimations of bilirubin levels that inform whether a TSB should be obtained (9). TCB measurements are noninvasive and reduce the need for blood sampling (10,11). Measurement of TSB by HPLC (High Performance Liquid Chromatography) is the gold standard requiring specialized laboratory equipment [12]. Nonetheless, there remains limitation in our facility in this regard. Recently developed low-cost point-of-care (POC) instruments only need a small amount of whole blood to measure total bilirubin. These POC instruments seem promising for LMICs, because not all facilities have access to laboratories for timely and accurate TSB measurements, and send blood samples to another hospital for analysis (4,12–15**)**. POC instruments are also cheaper than TCB devices and their measurements are reliable during phototherapy. The Bilistick®, a POC instrument had strong correlations (up to 0.96) with routine laboratory methods, using first generation devices (15). A Bilistick® System with updated firmware (BM-BS 1.0 – FW version 2.0.1) should have improved performance, avoiding errors or false-low test results [12,14]. This study compares diagnostic performance of the Bilistick® and TCB with routine laboratory TSB.

Methods

This was a prospective study conducted in Dr. Soetomo General Hospital, Surabaya, Indonesia for 7 months (from December 1st 2018 until June 30th 2019). Inclusion criteria consisted of clinical jaundice (any Kramer score > 0), a gestational age of ≥ 32 weeks and/or a birth weight of ≥ 1500 grams, and a postnatal age ≤14 days. Infants who received phototherapy (PT) in the preceding 24 hours, or with respiratory or circulatory insufficiency were excluded because PT results in bleaching of the skin, and respiratory or circulatory insufficiency may reduce skin perfusion and cause unreliable TCB measurements. Infants with severe congenital abnormalities were excluded because of ethical constraints preventing us from asking for informed consent.

TCB measurements were taken at the sternum using the JM-105 bilirubinometer (Dräger, Lübeck, Germany), repeated three times and then the mean TCB value was automatically calculated by the device. TCB measurement and heel-pricks for whole blood Bilistick® bilirubin measurements were taken simultaneously, while TSB was taken within an hour afterward. The Bilistick® measurement was done according to manufacturer's instructions using the Bilistick® System: reader model: BM-BS 1.0; production year: 2017; FW version: 2.0.1 (https://www.bilimetrix.net/bilistick-system). A Bilistick® test strip was inserted in a previously calibrated reader; 25 µL blood was obtained via a heel prick and collected in a pipette and transferred to the test strip. The Bilistick® may identify an error during measurement and display an error message, e.g., B04, that the serum has not properly entered the NC membrane, or T06, that the NC membrane did not reach optimal saturation within the test time. Measurements resulting in an error message were repeated once before being recording as an error. TSB was measured using a routine analytical diazo method on the SIEMENS Dimension® (Siemens Healthcare GmbH, Germany). The following patient data was recorded: gender, birth weight, gestational age, postnatal age (in days), and Kramer score.

The sample size sample size of our study corresponds with sample sizes of other cross-sectional prospective studies that compared different methods for predicting hyperbilirubinemia requiring treatment. Greco and colleagues included 161 infants, and 126 infants had paired Bilistick® and TSB test results; Rohsiswatmo and colleagues included 94 infants [12,16]. The data were analyzed using IBM SPSS Statistic Version 21.0 and Microsoft excel (Microsoft 365, version 1911) using Spearman correlation and linear

regression. Bland-Altman plots were also constructed for each pair to calculate mean differences (MD) and 95% limits of agreement (95% LoA): MD ± 1.96 SDs. The 95% LoA should contain the difference between the two methods for 95% of paired measurements. We calculated Sensitivity (Sn), Specificity (Sp), Positive Predictive Value (PPV), Negative Predictive Value (NPV), positive and negative likelihood ratios (LH+ and LH-, resp.) to predict significant hyperbilirubinemia, i.e., any TSB above treatment thresholds according to the Indonesian Guideline (http://yankes.kemkes.go.id/unduh/fileunduhan_1610349726_94555.pdf/16) (16).

Results

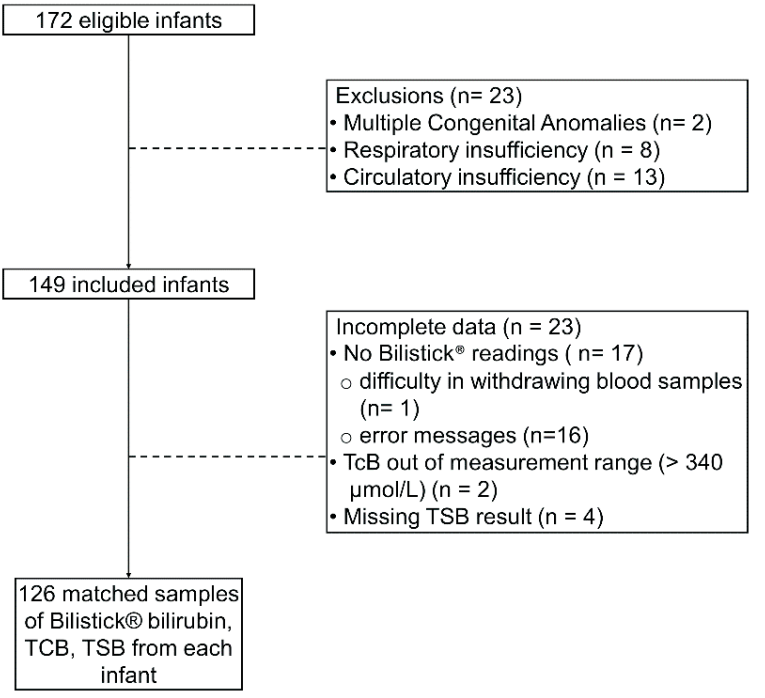

Figure 1. Sample Recruitment

There were 172 eligible infants during the seven-month study period; 23 were excluded (Figure 1). Twenty-three of the remaining 149 infants had incomplete data (Figure 1). The Bilistick® showed an error reading in 16 (10.7 %) infants (five times B04 and 11 times T06, respectively), and for one infant not enough blood was obtained. TCB was too high (i.e., > 340 µmol/L) to be reliably measured in two infants. Their TSB values were 362 µmol/L and 432 µmol/L, respectively. TSB results were missing in four infants. A total of 126 neonates had matched measurements of Bilistick® bilirubin, TCB, and TSB. Most of the infants (n=117) were admitted to our NICU or our neonatology ward at the time of measurements. Nine infants were included during their visit of the outpatient clinic as routine control after discharge. Table 1 shows that many infants were late preterm with a mean (± SD) birth weight of 2243 ± 610 g. Most infants presented at the fifth postnatal day with moderate jaundice (73.8% had a Kramer score of 2 or 3). The mean (± SD) POC Bilistick® bilirubin, TCB, and TSB values were 185 (± 65) µmol/L, 223 (± 42) µmol/L, and 196 (± 47) µmol/L, respectively. The relationship between POC Bilistick® bilirubin and TSB is presented in Figure 2A with a correlation coefficient of 0.738 ($p < 0.001$). The Bland Altmann plot shows four extreme outliers; the POC Bilistick® bilirubin values were very low. The POC Bilistick® bilirubin underestimated TSB with a mean difference (±SD) of -11 (± 46) µmol/L with a 95% CI of -18.98 to -2.81 µmol/L (Figure 2B). The 95% LoA were -100.79 to 78.99 µmol/L. Figure 2C shows the correlation between TCB and TSB with a correlation coefficient $r = 0.785$ ($p < 0.001$). TCB tended to overestimate TSB with a mean difference (± SD) of 26 (± 30) µmol/L with a 95% CI of 21 to 32 µmol/L. The 95% LoA were 33 to 86 µmol/L (Figure 2D).

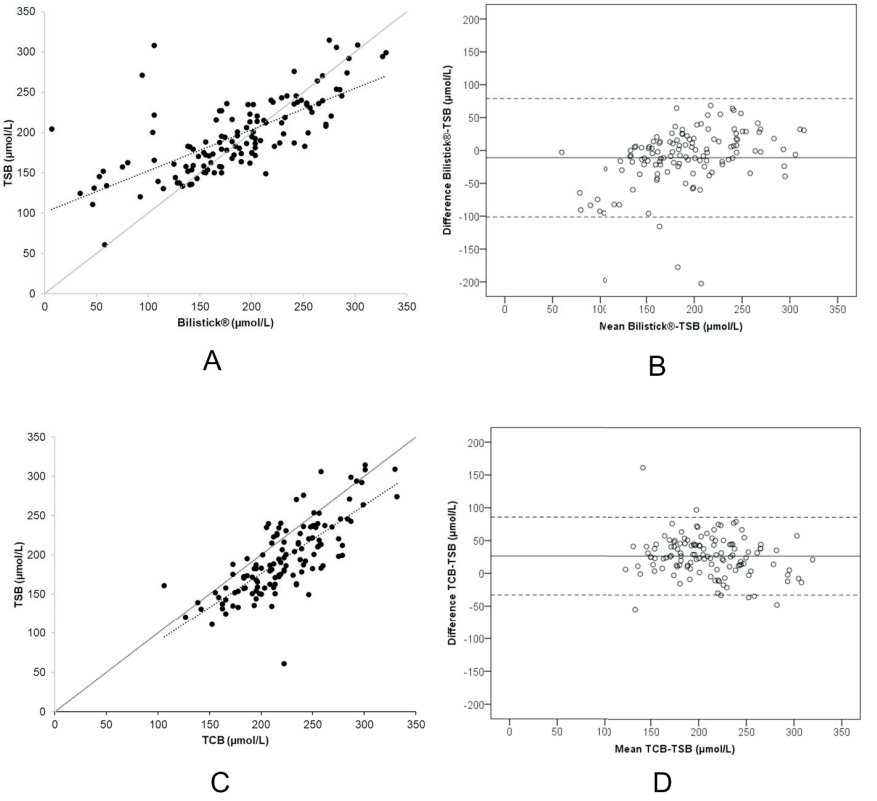

Figure 2. The correlation of Bilistick® System (BM-BS 1.0 – FW version 2.0.1) and TSB (A), the Bland Altman Plot of Bilistick® and TSB (B), the correlation of TCB and TSB (C) and the Bland Altman plot of TCB and TSB (D). The straight line in Figure 2A and 2C represents the line of identity; the dashed line in Figure 2A and 2C represents the trend line. The straight line in Figure 2B and 2D corresponds with the mean difference; the dashed lines in Figure 2B and 2D represent the limits of agreement.

Tables 2 and 3 show data of Bilistick® and TCB vs. laboratory TSB for all infants, and infants weighing < 2000 g, and ≥ 2000 g. Table 4 shows diagnostic accuracy parameters of TCB and Bilistick® to predict significant hyperbilirubinemia according to the Indonesian Hyperbilirubinemia Guideline. Diagnostic accuracy of TCB and Bilistick® was higher for infants weighing ≥ 2000 than for infants weighing < 2000, except for sensitivity. Overall, negative predictive values were 0.88 for Bilistick® and 0.95 for TCB. LH- was lowest for TCB (0.12) and LH+ was highest for Bilistick® (4.62). PPVs were 0.67 and 0.54 for Bilistick® and TCB, respectively.

Table 1. Clinical Characteristics and Bilirubin Parameters

Clinical Characteristic (n=126)	Value
Birth weight, g	2243 ± 610 [1500-4500]
Birth weight percentile	28 ± 27 [0-100]
Birth weight, g (%)	
1500-1999	53 (42)
≥2000	73 (58)
Gestational ages, weeks	35.5 ± 2 [32-41]
Gestational ages (%)	
32-37	105 (83.3)
37-42	21 (16.7)
Postnatal age, h	118± 68 [34-331]
Gender	
- Female	66 (52.4)
- Male	60 (47.6)
Hematocrit level,% (n=104)	47 ± 7 [31-64]
Kramer score	
- 1	14 (11.1)
- 2	52 (41.3)
- 3	41 (32.5)
- 4	18 (14.3)
- 5	1 (0.8)
Bilirubin parameters (µmol/L)	
TCB	223 ± 42 [106 -332]
POC Bilistick®	185 ± 65 [7-330]
TSB	196 ± 47 [61-315]

Data are expressed as mean ± SD [ranges] or n (%)

Table 2. Bilistick® accuracy to predict significant hyperbilirubinemia based on the Indonesian Hyperbilirubinemia Guideline

N(%)	TSB (+)	TSB (-)	Total
N= 126 (100)			
Bilistick® (+)	29	14	43
Bilistick® (-)	10	73	83
Total	39	87	126
N= 53 (42) < 2000 g			
Bilistick® (+)	15	10	25
Bilistick® (-)	5	23	28
Total	20	33	53
N= 73 (58) ≥ 2000 g			
Bilistick® (+)	14	4	18
Bilistick® (-)	5	50	55
Total	19	54	73

(+) indicates hyperbilirubinemia above treatment threshold of the Indonesian Hyperbilirubinemia Guideline; (-) indicates hyperbilirubinemia that needs no treatment according to the Indonesian Hyperbilirubinemia Guideline

Table 3. TCB accuracy to predict significant hyperbilirubinemia based on the Indonesian Hyperbilirubinemia Guideline

N(%)	TSB (+)	TSB (-)	Total
N= 126 (100)			
TCB (+)	36	31	67
TCB (-)	3	56	59
Total	39	87	126
N= 53 (42) BW < 2000 g			
TCB (+)	19	23	42
TCB (-)	1	10	11
Total	20	33	53
N= 73 (58) BW ≥ 2000 g			
TCB (+)	17	8	25
TCB (-)	2	46	48
Total	19	54	73

(+) indicates hyperbilirubinemia above treatment threshold of the Indonesian Hyperbilirubinemia Guideline; (-) indicates hyperbilirubinemia that needs no treatment according to the Indonesian Hyperbilirubinemia Guideline

Table 4. Accuracy parameters of TCB and Bilistick® based on birth weight

Birth weight (g)	Sensitivity	Specificity	PPV	NPV	LH (+)	LH (-)
Bilistick®						
< 2000	0.75	0.70	0.60	0.82	2.48	0.36
≥ 2000	0.74	0.93	0.78	0.91	9.95	0.28
Overall	0.74	0.84	0.67	0.88	4.62	0.31
TCB						
< 2000	0.95	0.30	0.45	0.91	1.36	0.17
≥ 2000	0.89	0.85	0.68	0.96	6.04	0.12
Overall	0.92	0.64	0.54	0.95	2.59	0.12

PPV: Positive Predictive Value; NPV: Negative Predictive Value; LH (+), positive likelihood ratio, LH (-), negative likelihood ratio.

Discussion

This study demonstrated that both Bilistick® and TCB show a strong and statistically significant correlation with TSB. Bilistick® underestimates TSB with a mean difference (±SD) of -11 (± 46) µmol/L with rather broad LoA of -101 to 79 µmol/L. In contrast, TCB with the JM-105 bilirubinometer tends to overestimate TSB with a mean difference (±SD) of 26.44 (± 30.31) µmol/L with corresponding LoA of -33 to 86 µmol/L. Apart from sensitivity, diagnostic properties of Bilistick® System (BM-BS 1.0 – FW version 2.0.1) and JM-105 bilirubinometer are slightly better in infants weighing ≥ 2000 g. Overall, the Bilistick® has lower sensitivity and higher negative likelihood ratio when compared with TCB. In contrast, Bilistick® has higher specificity and higher positive likelihood ratio when compared with TCB in all infants. The NPV of the Bilistick® is lower than the NPV of the JM-105 bilirubinometer. If treatment decisions would have been based on the Bilistick®, then 10 out of 39 infants who needed treatment would have been missed. TCB with the JM-105 bilirubinometer would have missed three out of 39 infants.

We found a strong correlation between TCB and TSB in accordance with previous studies (10). A recent Indonesian study reported higher correlations between TCB and TSB in preterm infants before and after 24h and 48h of phototherapy (17). In our study, we demonstrated that TCB with the JM-105 overestimates TSB with a mean difference (± SD) of 26 (± 30) µmol/L and LoA of -33 to 86 µmol/L before or 24h after phototherapy. A study in India that evaluated TCB with the same instrument in infants > 34 weeks showed a somewhat higher correlation between TCB and TSB than we found, i.e., 0.89, and 0.93 at the age of 24h and of 48h. As in our study, TCB overestimated TSB with 26 µmol/L at 24h and 21 µmol/L at 48h (18). Greco et al. reported that TCB measured before or during phototherapy with the JM-103 overestimated TSB with a mean difference of 5 (± 50) µmol/L and corresponding LoA from **-92 to 103** µmol/L **(13)**. Data on the relationship between TCB and TSB after discontinuation of PT show good correlation after 8 hours. TCB is therefore considered a reliable method for early identification of (rebound) hyperbilirubinemia in preterm, near-term, and term neonates before and after phototherapy. Due to its tendency to overestimate TSB it is unlikely to miss an infant with a TSB level that should be treated. However, over-estimation is not a desirable feature, because this may lead to unnecessary blood sampling. TCB can also underestimate

the correct TSB level so cut off rules are recommended (19), such as adding 50 μmol/L to the obtained TCB measurement. In other words, when TCB is within 50 μmol/L of the treatment threshold, TSB should be obtained to correct for falsely low readings (20,21).

We evaluated whether the problems of the first generation Bilistick® were overcome after an update of its firmware. In contrast to TCB with the JM-105 bilirubinometer, the Bilistick® System (BM-BS 1.0 – FW version 2.0.1) underestimates TSB, in near-term and preterm infants. Previous data showed that the Bilistick® slightly underestimated TSB in 118 near-term newborn infants with a mean difference of -10 μmol/L. Zabetta et al. concluded in 2013 that the Bilistick® 1.0 was an effective method to screen bilirubin levels in jaundiced newborns, but also to identify infants at risk for kernicterus (15). It was acknowledged that technical errors may occur when Hct levels are above the threshold maximum Hct of 65% resulting in insufficient saturation of the test strip membrane. Greco et al in 2017 excluded 35 (22%) of 161 enrolled infants; 11 (6.8%) due to technical failure of the Bilistick®. The Bilistick® underestimated TSB with a mean (±SD) difference of -22 (±39) μmol/L, with corresponding LoA from -100 to 56 μmol/L (13). Falsely low Bilistick® values have been documented in a large study in four different countries that analyzed its performance (22). This study confirmed that Bilistick® values slightly underestimate TSB (-17.1 μmol/L over a TSB range from 17.1 to 684 μmol/L). There were 1230 infants who did not require treatment according to Bilistick® readings, whereas 88 (7.2%) of them reached treatment threshold according to TSB (22). Thielemans et al. reported error messages in 48.6% of 173 Bilistick® tests. They concluded that Bilistick® 1.0 was not suitable for clinical conditions, because of its failure rate and false-negative readings, which would result in undertreatment in 4 out of 5 infants when tested with a Hct value > 55% at a humidity ≥75% (23). Rohsiswatmo compared the 1st generation Bilistick® (2016) with laboratory TSB in 94 preterm infants in Indonesian climate conditions and found that Bilistick® underestimated TSB; 11 out of 94 infants (12%) would not have received treatment, relying on Bilistick® readings alone (17). After the five studies evaluating the performance of the first version of the Bilistick®, a version with updated firmware was launched. Our study is the first study that has evaluated the performance of the

Bilistick® System with updated firmware (BM-BS 1.0 – FW version 2.0.1). We found a lower correlation between TSB and the Bilistick® compared with previous studies (13,15,17,22,23). Ten newborns reached the PT threshold as determined by TSB measurement, but had low POC Bilistick® bilirubin readings. Solely relying on POC bilirubin measurement with the Bilistick® might have resulted in a delay of phototherapy. Around 10.7% of the measurements resulted in error messages, and in four cases the device showed extremely low values compared to the TSB value up to – 203 µmol/L (Figure 2B). The manual indicates that unpredictable low readings can result from not enough blood on the measurement strip. Unfortunately, in these cases no error message appears.

We acknowledge several limitations of our study. The current study is composed of a convenient sample size (similar to that of other studies) using a BS 1.0 with the highest firmware version possible. To the best of our knowledge, data from the recently launched second generation of the **Bilistick® S**ystem with novel firmware (BS 2.0 - FW version 4.0.36) and test strips are not available yet. Next, blood for laboratory TSB measurement was not taken simultaneously with TCB and **Bilistick®** measurements, which could have affected calculated diagnostic properties. However, blood for laboratory TSB was taken within one hour after these measurements to minimize discrepancies. Finally, we did not apply a decision rule for TCB to correct for underestimation of TSB.

Conclusion

In conclusion, TCB is a valuable screening tool for neonatal jaundice in Indonesian newborn infants. The reported overestimation makes it very unlikely to miss an infant with a TSB level that should be treated. The Bilistick® System (BM-BS 1.0 – FW version 2.0.1) underestimates TSB values compared to laboratory measurements. In our study, it also lacked similar diagnostic properties when compared to TCB to serve as a reliable screening instrument for neonatal hyperbilirubinemia. Use of this promising and fast bedside technique has the risk for falsely low readings. Further improvement of Bilistick®'s diagnostic accuracy and validation in a wide variety of populations and settings, not strictly limited to LMICs, is essential.

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Statement of Ethics

The author(s) have no ethical conflicts to disclose. The study was approved by Dr. Soetomo General Hospital Surabaya Ethics Committee no 0526/KEPK/VIII/2018. Informed consent was obtained from parents or legal guardians.

Disclosure Statement

The authors have no conflicts of interest to declare

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Author Contributions

Mahendra T.A. Sampurna, Pieter J.J. Sauer, Arend F. Bos, Peter H. Dijk, Christian V. Hulzebos: Conceived and designed the experiments, analyzed and interpreted the data, wrote and critically reviewed and revised the paper.

Siti A. D. Rani: Performed the experiments, analyzed and interpreted the data, revised the paper.

References

1. Bhutani VK, Stark AR, Lazzeroni LC, Poland R, Gourley GR, Kazmierczak S, et al. Predischarge screening for severe neonatal hyperbilirubinemia identifies infants who need phototherapy. J Pediatr 2013;162:477-482. e1. https://doi.org/10.1016/j.jpeds.2012.08.022.

2. Slusher TM, Zipursky A, Bhutani VK. A Global Need for Affordable Neonatal Jaundice Technologies. Semin Perinatol 2011;35:185–91. https://doi.org/10.1053/j.semperi.2011.02.014.
3. Olusanya BO, Ogunlesi TA, Slusher TM. Why is kernicterus still a major cause of death and disability in low-income and middle-income countries? Arch Dis Child 2014;99:1117–21. https://doi.org/10.1136/archdischild-2013-305506.
4. Greco C, Arnolda G, Boo NY, Iskander IF, Okolo AA, Rohsiswatmo R, et al. Neonatal Jaundice in Low- and Middle-Income Countries: Lessons and Future Directions from the 2015 Don Ostrow Trieste Yellow Retreat. Neonatology 2016;110:172–80. https://doi.org/10.1159/000445708.
5. Kramer LI. Advancement of dermal icterus in the jaundiced newborn. Am J Dis Child 1969;118:454–8. https://doi.org/10.1001/archpedi.1969.02100040456007.
6. Keren R, Tremont K, Luan X, Cnaan A. Visual assessment of jaundice in term and late preterm infants. Arch Dis Child Fetal Neonatal Ed 2009;94:F317–22. https://doi.org/10.1136/adc.2008.150714.
7. Sampurna MTA, Ratnasari KA, Etika R, Hulzebos C V., Dijk PH, Bos AF, et al. Adherence to hyperbilirubinemia guidelines by midwives, general practitioners, and pediatricians in Indonesia. PLoS One 2018;13:e0196076. https://doi.org/10.1371/journal.pone.0196076.
8. Davidson LT, Merritt KK, Weech AA. Hyperbilirubinemia in the Newborn. Am J Dis Child 1941;61:958–80. https://doi.org/10.1001/archpedi.1941.02000110046005.
9. Maisels MJ, Bhutani VK, Bogen D, Newman TB, Stark AR, Watchko JF. Hyperbilirubinemia in the newborn infant ≥35 weeks' gestation: An update with clarifications. Pediatrics 2009;124:1193–8. https://doi.org/10.1542/peds.2009-0329.
10. Nagar G, Vandermeer B, Campbell S, Kumar M. Reliability of transcutaneous bilirubin devices in preterm infants: A systematic review. Pediatrics 2013;132:871–81. https://doi.org/10.1542/peds.2013-1713.
11. Grabenhenrich J, Grabenhenrich L, Bührer C, Berns M. Transcutaneous bilirubin after phototherapy in term and preterm infants. Pediatrics 2014;134:e1324–9. https://doi.org/10.1542/peds.2014-1677.
12. Muraca M, Blanckaert N. Liquid-chromatographic assay and identification of mono- and diester conjugates of bilirubin in normal serum. Clin Chem 1983;29:1767–71. https://doi.org/10.1093/clinchem/29.10.1767.

13. Greco C, Iskander IF, Akmal DM, El Houchi SZ, Khairy DA, Bedogni G, et al. Comparison between Bilistick System and transcutaneous bilirubin in assessing total bilirubin serum concentration in jaundiced newborns. J Perinatol 2017;37:1028–31. https://doi.org/10.1038/jp.2017.94.
14. Keahey PA, Simeral ML, Schroder KJ, Bond MM, Mtenthaonnga PJ, Miros RH, et al. Point-of-care device to diagnose and monitor neonatal jaundice in low-resource settings. Proc Natl Acad Sci U S A 2017;114:E10965–71. https://doi.org/10.1073/pnas.1714020114.
15. Zabetta CDC, Iskander IF, Greco C, Bellarosa C, Demarini S, Tiribelli C, et al. Bilistick: A low-cost point-of-care system to measure total plasma bilirubin. Neonatology 2013;103:177–81. https://doi.org/10.1159/000345425.
16. Kementerian Kesehatan RI. Pedoman Nasional Pelayanan Kedokteran Tata Laksana Hiperbilirubinemia. Indonesia: 2019.
17. Rohsiswatmo R, Oswari H, Amandito R, Sjakti HA, Windiastuti E, Roeslani RD, et al. Agreement test of transcutaneous bilirubin and bilistick with serum bilirubin in preterm infants receiving phototherapy. BMC Pediatr 2018;18:315. https://doi.org/10.1186/s12887-018-1290-9.
18. Varughese PM. Kramer's scale or transcutaneous bilirubinometry: the ideal choice of a pediatrician? can we trust our eyes? Int J Contemp Pediatr 2019;6:1794–801. https://doi.org/10.18203/2349-3291.ijcp20193702.
19. Taylor JA, Burgos AE, Flaherman V, Chung EK, Simpson EA, Goyal NK, et al. Utility of decision rules for transcutaneous bilirubin measurements. Pediatrics 2016;137. https://doi.org/10.1542/peds.2015-3032.
20. Hulzebos C V., Imhoff DEV Van, Bos AF, Dijk PH. Should transcutaneous bilirubin be measured in preterm infants receiving phototherapy? the relationship between transcutaneous and total serum bilirubin in preterm infants with and without phototherapy. PLoS One 2019;14:e0218131. https://doi.org/10.1371/journal.pone.0218131.
21. Van Den Esker-Jonker B, Boer L Den, Pepping RMC, Bekhof J. Transcutaneous bilirubinometry in jaundiced neonates: A randomized controlled trial. Pediatrics 2016;138:e20162414. https://doi.org/10.1542/peds.2016-2414.

22. Greco C, Iskander IF, El Houchi SZ, Rohsiswatmo R, Rundjan L, Ogala WN, et al. Diagnostic Performance Analysis of the Point-of-Care Bilistick System in Identifying Severe Neonatal Hyperbilirubinemia by a Multi-Country Approach. EClinicalMedicine 2018;1:14–20. https://doi.org/10.1016/j.eclinm.2018.06.003.
24. Thielemans L, Hashmi A, Priscilla DD, Kho Paw M, Pimolsorntong T, Ngerseng T, et al. Laboratory validation and field usability assessment of a point-of-care test for serum bilirubin levels in neonates in a tropical setting. Wellcome Open Res 2018;3:110. https://doi.org/10.12688/wellcomeopenres.14767.1.