INFORMATION BRIEF (RAPID REVIEW)

[redacted] A NON-INVASIVE JAUNDICE METER

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
014/2023

IPT Mark
Rapid Review
INAHTA

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Government Office Complex
62590, Putrajaya
Tel: 603 8883 1229

Available online via the official Ministry of Health Malaysia website: http://www.moh.gov.my

SUGGESTED CITATION: Arif I, Roza S and Izzuna MMG. [redacted] – A non-invasive jaundice meter. Information Brief. Ministry of Health Malaysia: Malaysian Health Technology Assessment Section (MaHTAS); 2023. 8 pages. Report No.: 014/2023

DISCLOSURE: The author of this report has no competing interest in this subject and the preparation of this report is entirely funded by the Ministry of Health Malaysia.

TITLE: NEORUBIN – A NON-INVASIVE JAUNDICE METER

PURPOSE

To provide evidence summary on the safety, effectiveness and cost-effectiveness of [redacted] a non-invasive bilirubinometer developed by a local company. This is based upon request from the Deputy Director of Medical Division, State Health Department (JKN) Selangor following proposal from the company to introduce [redacted] in the healthcare facilities.

BACKGROUND

Neonatal jaundice (NNJ), also known as neonatal hyperbilirubinemia is one of the common medical conditions among newborn babies. It commonly occurs in approximately 65% of all full term babies with the peak bilirubin levels occurring on day 5 of life.[1] It is resulted from a predisposition to the production of bilirubin and newborn's limited ability to excrete it.[1] Jaundice is clinically detectable when the serum bilirubin levels area > 85 umol/L.[1] Active screening of newborns at risk for neonatal jaundice is recommended in major international guidelines.[2,3] While most cases of neonatal jaundice are physiological and resolved spontaneously, [1,4] certain risk factors can lead to severe jaundice including inadequate feeding, premature babies, low birth weight and ABO O positive mothers. [1]

There are several methods of monitoring jaundice in newborns. Gold standard for neonatal hyperbilirubinemia monitoring is by total serum bilirubin measurements. [1, 2, 4] This involves blood sampling from the newborn before measurement is done in the laboratory using various methods such as performance liquid chromatogprahy (HPLC), Diazo-based methods or capillary electrophoresis.[1, 4, 5] The conventional blood taking procedure for obtaining serum bilirubin, which may be repeated several times can be painful to the newborn, carries risk of infection, is costly and time consuming. [5, 7] Other less invasive methods for detecting neonatal jaundice have been developed to assist healthcare workers in clinical setting including visual assessment of neonatal jaundice (Kramer's Rule) and transcutaneous bilirubinometer. [1]

Transcutaneous bilirubinometer (TcB), also known as jaundice meter was introduced since 1980s and ever since has been widely used as important screening tool for hyperbilirubinemia in management worldwide. [6] The American Academy of Paediatrics recommends a pre-discharge bilirubin level monitoring by either obtaining serum or transcutaneous bilirubin reading. [8] However, TcB application in clinical setting has its own limitation. TcB can overestimate or underestimate the bilirubin concentration when compared to serum bilirubin. This underestimation can lead to undertreatment of babies at risk for severe hyperbilirubinemia. [1] In preterm infants, transcutaneous bilirubin measurements may be less accurate due to immature skin and a different albumin-to-bilirubin binding in premature infant. Other factors including races and body weight may also decrease its accuracy. [12] Transcutaneous bilirubinometer have been widely used especially in high-income countries for screening of neonatal jaundice as it is not only cheap, painless but also with minimal risk / adverse events. [14]

TECHNICAL FEATURES

Transcutaneous bilirubinometer works by directing light into the skin of a newborn and measures the intensity of specific wavelength that is returned to the device. The number of wavelengths used is variable in different type of transcutaneous bilirubinometer. The spectra of the returned light will depend on concentration of various cutaneous components including bilirubin, hemoglobin, melanin and collagen of which has difference light absorption levels. These optical signals then are converted to electrical signal by a photocell. This principle allows calculation of bilirubin concentration through the reflected light analysis using a device-specific algorithm and a microcomputer in many of transcutaneous bilirubinometer device available today including [redacted]evice. [13] Preferred sites for measurements are forehead and upper end of the sternum. Readings on hyperemic area, bruises, birthmarks or subcutaneous hematoma should be avoided as it may affect the results. [13] The overall process of obtaining bilirubin level through transcutaneous bilirubinometer is non-invasive. [13]

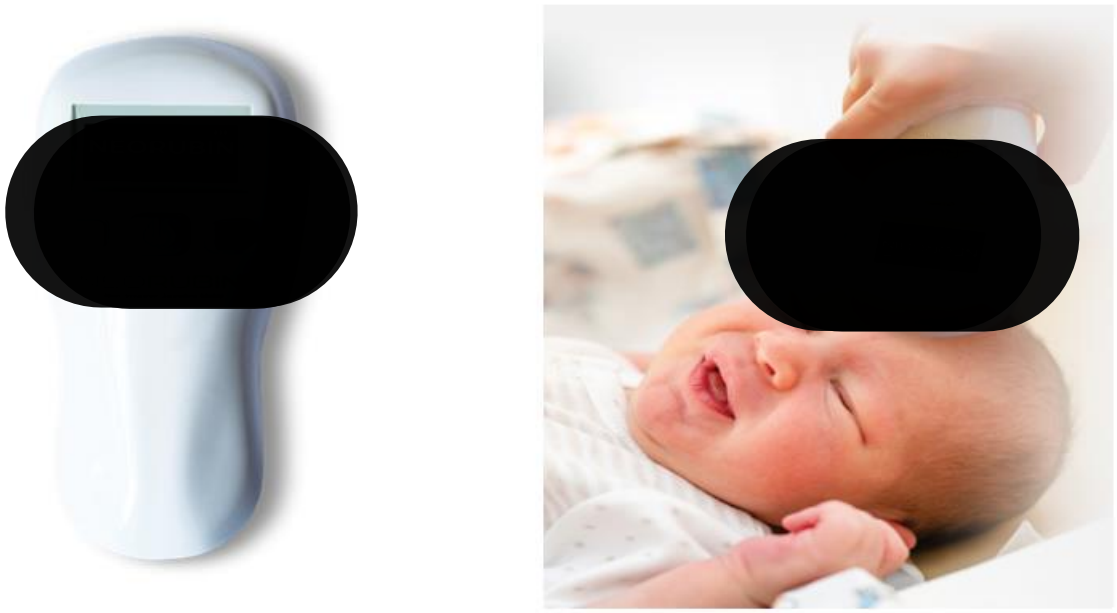

Figure 1[redacted] (Left) and application o[redacted]Right)

Based on information obtained provided by the company, [redacted] has the measurement range of 0 mmol/L to 307.80 mmol/L for detection of bilirubin. Based on comparison with other types of TcB such as Drager JM-105, the detection of bilirubin levels ranged from 0-340 mmol/L. [redacted] said to be almost similar with other type of TcB available in Malaysia. The results during measurement using [redacted] is available within three seconds and can be printed via wireless printer. It does not require any disposable material throughout the process of measuring transcutaneous bilirubin levels. The device is said to have a shelf life of five years.

EVIDENCE SUMMARY

A total of 178 titles were retrieved from the scientific databases such as Medline, EBM Reviews, EMBASE via OVID, PubMed and from the general search engines [Google Scholar]. Search was limited to articles published from year 2003 onwards in English language. Additional articles were identified from reviewing the references of retrieved articles. Studies with less than 30 subjects were excluded.

Earlier review by MaHTAS (2009) on TcB found that the device was effective in estimation of serum bilirubin in term neonates. However, there was insufficient evidence to show the effectiveness of TcB in estimating serum bilirubin in preterm neonates. They also found that sternum readings were found to correlate better with total serum bilirubin values than forehead readings. However, a confirmation with chemistry analyzer in clinical laboratories was emphasized. [17]

Four studies were found to be relevant and included in this review, which comprised of cohort analysis (three) and cost-minimization analysis (one).

SAFETY

The Medical Device Authority (MDA) Malaysia has approve[redacted]s a non-invasive transcutaneous bilirubinometer to screen for diagnosis of hyperbilirubinemia in conjunction with clinical signs and laboratory measurements. [15] No information obtained on its approval from other regulatory bodies.

There was no evidence retrieved on safety of [redacted] in measuring transcutaneous bilirubin among newborns. Based on clinical trial done by the company involving 265 newborns, there was one reported adverse event unrelated to the use of device during study. The adverse event was reported as suspect ERB Duchenne palsy

EFFECTIVENESS

There was no evidence retrieved on effectiveness o[redacted]rom the scientific databases.

A study was conducted by Ruziaton et al. (2020) to evaluate the accuracy of their product in comparison to Drager JM-103 and conventional serum bilirubin measurements in infants diagnosed with jaundice in Malaysia. The study was conducted in 2020 with data collection done in Klinik Kesihatan Pandamaran, Klang. The study involved two stages process. In stage I, a total of 250 samples were obtained where each sample will have 10 readings from NEORUBIN, one reading from Drager and one blood sample. This data obtained from this stage was used to configure the software algorithm of the device in preparation for stage II. In the later stage, a total of 265 samples were included, where all samples required one reading from each NEORUBIN, Drager and blood sample. Exclusion criteria in this study were TsB > 13.4 mg/dL at screening and child with hydrops fetalis.

They found the mean serum bilirubin levels recorded by test device was 10.93 mg/dL (SD 5.84) in comparison to Drager [9.85 mg/dL, (SD 2.24)] and serum bilirubin [Mean 11.15 mg/dL, (SD 2.63)]. The accuracy of test device in comparison to gold standard was 86.4% (95% CI, 81.7 to 90.3) while Drager had an accuracy of 94.7% (95% CI, 91.8% to 97.4). Both test and Drager devices have almost similar positive predictive value of 97% (95% CI, 96.9 to 97.2) and 97.7% (95% CI, 96.9 to 98.3)) respectively. However, the study showed that negative predictive value of index test was 0% in comparison to Drager of 12.5% (95% CI, 1.98 to 50.3). The sensitivity of test device was found to be lower in comparison to Drager in this study. It is reported that sensitivity of test device was 88.8% (95% CI, 84.3 to 92.3) while Drager 97.3% (95% CI, 94.5 to 98.9).

A subgroup analysis of remaining 183 samples after reconfiguration was done found out that the accuracy of test device increased up to 96.2% (95% CI, 92.3 to 98.5). The sensitivity of test device also increased to 99.4% (95% CI, 96.9 to 100) with positive predictive value of 96.7% (95% CI, 96.6 to 96.7%). Pearson correlation statistical test between the reconfigured data set by NEORUBIN meter and serum blood bilirubin levels found a positive correlation, r = 0.5041 with p value < 0.0001.

Wickremasinghe et al. (2012) in another prospective cohort study also found that, after introduction of TcB as screening to determine the need of TSB, there was a significant reduction in TSB blood draw rate for inpatient and outpatient newborns, by 6% and 16% respectively ($p < 0.02$ and $p < 0.001$ respectively). The new screening protocol has also led to a reduced rate of overall phototherapy usage by 34% ($p < 0.001$) and phototherapy use utilization on inpatients by 56% ($p <0.001$). However, there was associated increased in rate of infant readmission for phototherapy by 39% (18-25 admission per 1000 newborns, $p < 0.05$) after new screening protocol has been implemented. The direct cost of serum bilirubin estimated to be 20 US dollar while TcB at 8 US dollar at the time of study being conducted.

COST-EFFECTIVENESS

No evidence retrieved on cost-effectiveness o[redacted]or the detection of hyperbilirubinemia in newborn. Estimated price per device is said aroun[redacted]. Estimated price of other type of TcB are aroun[redacted]hile [redacted] around [redacted]o disposable items required on using both [redacted] whil[redacted]equires a Bilical cap for each test costing aroun[redacted] [16,17]

Stephanie et al. (2018) conducted a cost-minimization analysis for transcutaneous screening versus total serum bilirubin measurement for newborn jaundice in hospital and community setting over a period of six months. They conducted a study to estimate cost associated with a single serum bilirubin screen (TSB program) and a single transcutaneous bilirubinometry screen prior decision to take serum bilirubin measurement (TcB-TSB program) by accounting to variability including time taken to screen, travel time, mileage, laboratory expenses and disposables used. In the study, the estimated cost per TcB screen in hospital and community (urban and rural) were $3.54 and $3.76 respectively, whereas the cost per TSB screen was $15.82 in hospital setting and $50.21-$65.03 in urban to rural community settings. They found that the estimated total reduction of cost was up to 31.7% when TcB-TSB program was

carried out in comparison to TSB program alone (TSB $82336, TcB-TSB $56159).

In another prospective cohort study conducted by Stephen W et al. (2012) to determine resource utilization with transcutaneous bilirubinometry program, there was a significant reduction (54.9%, $p < 0.001$) in the incidence of severe initial TSB values (>342 mmol/L) in the community after the introduction of TcB device as screening methods among newborn. The frequency of TSB measurements done in the community also declined by 22.9% from 134.4 to 103.6 blood drawn per 1000 live births for the 8 months period of study with implementation of TcB program (OR: 1.33, CI 1.23-1.45, $p < 0.001$). They also found that the were significant reductions in avoidable TSB draws post implementation of TcB measurements at various threshold points (hours of life of the newborn) ranging from 40.6% – 73.4% reduction. However, there was no significant changes in initial nursery length of stay among newborn with the implementation of Tcb ($p = 0.1$).

CONCLUSION

In general, the use of transcutaneous bilirubinometer has been widely in used most medical facilities including those in Malaysia. There were limited evidences retrieved on the safety, effectiveness and cost-effectiveness o[redacted]n the detection of hyperbilirubinemia among newborn. Evidence based on a study provided by the company demonstrated its accuracy of 86.4% (95% CI, 81.7 to 90.3) and sensitivity of 88.8% (95% CI, 84.3 to 92.3). A subgroup analysis following reconfiguration of the device showed improved accuracy of 96.2% (95% CI, 92.3 to 98.5) and sensitivity of 99.4% (95% CI, 96.9 to 100). No safety issue related to this device was noted. Multiple evidences showed TcB-TSB program would reduce the cost in comparison to TSB program alone. Although it appeared safe, effective and cost-effective in comparison with other types of TcB in the market, further research is recommended.

REFERENCES

1. Clinical Practice Guidelines: Management of neonatal jaundice, 2nd edition 2014. MOH/P/PAK/288.15(GU)
2. Jeffrey M, Richard D, Vinod K, et al. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2004.114(1): 297-316.
3. Barrington KJ, Sankaran K, et al. Guidelines for detection, management and prevention of hyperbilirubinemia in term and late preterm newborn infants. Paediatric & child health 2007. 12(5): 401-418.
4. Okwundu CL, Olowoyeye A, Uthman OA, et al. Transcutaneous bilirubinometry versus total serum bilirubin measurement for newborns. Cochrane database of systematic reviews 2023. 5: CD012660.
5. Bernice VD, Lieve DB, Pepping RMC, et al. Transcutaneous bilirubinometry in jaundiced neonataes: A randomized controlled trial. Pediatrics 2016. 138(6): E20162414.
6. Mohamed M, Ibrahim NR, Ramli, et al. A comparison between the transcutaneous and total serum bilirubin measurement in Malay neonates with neonatal jaundice. Malays J Med Sci 2022. 29(1): 43-54.

7. Taylor JA, Burgos AE, et al. Discrepancies between transcutaneous and serum bilirubin measurements. Pediatrics 2015. 135(2):224-231.
8. Subcommittee on hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2004. 114(1): 297-316.
9. Fonseca R, Kyralessa R, et al. Covered skin transcutaneous bilirubin estimation in comparable with serum bilirubin during and after phototherapy. Journal of Perinatology 2012. 32(2): 129-131.
10. Tan KL, Dong F, et al. Transcutaneous bilirubinometry during and after phototherapy. Acta paediatrica 2003. 92(3): 327-331.
11. Nagar G, Vandermeer B, et al. Effect of Phototherapy on the Reliability of Transcutaneous Bilirubin Devices in Term and Near-Term Infants: A Systematic Review and Meta-Analysis. Neonatology 2016. 109(3): 203-212.
12. Karen T, Bucher HU, et al. Comparison of a new transcutaneous bilirubinometer (Bilimed) with serum bilirubin measurements in preterm and full-term infants. BMC Pediatr. 2009. 12:9:70.
13. Engle WD, Jackson GL, Engle NG. Transcutaneous bilirubinometry. Semin Perinatol 2014. 38(7): 438-451.
14. Dani C, Hulzebos CV, Tiribelli C. Transcutaneous bilirubin measurements: useful, but also reproducible? Pediatr Res. 2021. 89(4): 725-726.
15. [redacted]
16. Robertson A, Kazmierczak S, et al. Improved transcutaneous bilirubinometry: comparison of SpectR(X) BiliCheck and Minolta Jaundice Meter JM-102 for estimating total serum bilirubin in a normal newborn population. J Perinatol. 2002. 22(1):12-14.
17. Mariammah K. Non-invasive, hand held transcutaneous bilirubinometer. Health technology assessment section, medical development division, Ministry of health Malaysia 2009. 022/09.
18. McClean S, Baerg K, et al. Cost savings with transcutaneous screening versus total serum bilirubin measurement for newborn jaundice in hospital and community settings: a cost-minimization analysis. CMAJ Open 2018. 6(3): E285-E291
19. Wainer S, Parmar SM, et al. Impact of a transcutaneous bilirubinometry program on resource utilization and severe hyperbilirubinemia. Pediatrics 2012. 129(1): 77-86.
20. Wickremasinghe AC, Karon BS, Saenger AK, Cook WJ. Effect of universal neonatal transcutaneous bilirubin screening on blood draws for bilirubin analysis and phototherapy usage. Journal of Perinatol 2012. 32(11): 851-5.

Prepared by

Dr. Muhammad Arif Izzani
Medical Officer
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Reviewed by

Dr. Roza Sarimin
Public Health Physician
Senior Principal Assistant Director
Head of Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Dr. Izzuna Mudla Mohamed Ghazali
Public Health Physician & Deputy Director
Head of Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

20 December 2023