Diagnostic accuracy of transcutaneous bilirubinometer devices compared with the total serum bilirubin measurement in preterm (≤35 weeks) very low birth weight neonates during the neonatal period up to 7 days of life

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Abstract

Introduction: Hyperbilirubinaemia is the commonest morbidity in preterm neonates, most of whom are of very low birthweight (VLBW ≤1500g) babies. Repeated blood sampling in preterm VLBW neonates not only causes pain but may lead to sepsis and anaemia. Transcutaneous measurement of bilirubin by a device called transcutaneous bilirubinometer (TcB) is an effective alternative tool to predict neonatal hyperbilirubinaemia in late preterm and term neonates, most of whom have birthweights >2000g.

Objectives: To evaluate diagnostic accuracy of TcB devices in comparison to total serum bilirubin (TSB) measurements in VLBW neonates.

Method: We evaluated 128 preterm neonates with gestational ages ranging from 28 to 35 weeks and birthweights ≤1500g till 7 days of post-natal age. A total of 1003 TcB readings were taken, along with concurrent heel prick capillary samples, for laboratory measurement of TSB. For TcB, Drager JM-103 transcutaneous bilirubinometer was used and for TSB, Microlab's Easybil instrument was used. Coefficient of correlation (r) and Bland-Altman plot were calculated to check correlation between TSB and TcB.

Results: Total number of neonates was divided into 2 groups: i) ≤1000g and ii) 1001-1500g. Paired readings of TSB and TcB were taken before and after starting phototherapy. All the paired readings were analysed for correlation between TcB and TSB. Correlation co-efficient (r) value for group i) was 0.87 and for group ii) was 0.89 ($p<0.0001$). Before and after starting phototherapy, readings were analysed separately to see the effect of phototherapy on correlation between TcB and TSB. Correlation co-efficient (r) values for paired readings before starting phototherapy were 0.97 & 0.90 respectively for both groups and for paired readings after starting phototherapy were 0.81 & 0.83 respectively for both groups.

Conclusions: TcB measurements correlate significantly with TSB levels in early preterm neonates with VLBW. Phototherapy does not affect the correlation significantly.

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(Key words: Hyperbilirubinaemia, preterm neonate, transcutaneous bilirubin, VLBW)

Introduction

Preterm neonates are more at risk for hyperbilirubinaemia due to immature hepatic function, polycythaemia, delay in starting feeds, sepsis, etc.[1,2]. Hyperbilirubinaemia is potentially more dangerous in premature VLBW (birthweight ≤1500g) neonates due to the immature blood brain barrier which can lead to bilirubin induced neuronal damage[3]. Rough bilirubin estimation can be made visually as neonatal hyperbilirubinaemia progresses cephalocaudally[3]. However, recent studies showed that visual assessment correlates poorly with SB[3,4,5]. Blood sampling to estimate SB is the commonest investigation done in the neonatal intensive care unit (NICU)[6]. This is frequently performed by heel prick, a painful procedure with long-term sequelae. Therefore, an accurate non-invasive method of SB estimation is required. Transcutaneous estimation of bilirubin by a hand-held device called transcutaneous bilirubinometer (TcB) uses the principle of reflectance photometry and colorimetry[7]. TcB devices estimate SB by directing light into the neonatal skin and measuring the intensity of specific wavelengths[7]. There are several devices for transcutaneous estimation of bilirubin like "Bili Med", "Drager JM-102". "Drager JM-103", "Drager JM-105". We used "Drager JM-103" for current study. These devices correlated well with SB in term and near-term neonates in various studies[1-2,8-10]. Most neonates in these groups were of birthweight >2000g. American Academy of Pediatrics recommends utilisation of TcB devices for evaluating jaundice in infants >35 weeks' gestation[11]. However, the

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accuracy of TcB devices for estimating SB in preterm (≤35 weeks) VLBW neonates remains unclear[12-15].

Objectives

To evaluate diagnostic accuracy of TcB devices in comparison to total serum bilirubin (TSB) measurements in VLBW neonates.

Method

This was a time bound prospective cohort study done at the Department of Paediatrics at SSG Hospital and Medical College, Baroda from January to October 2017 after obtaining approval from the Institutional Ethical Committee on Human Research. We included VLBW neonates till 7 days of postnatal age with jaundice. All the VLBW neonates in our study were preterm babies of ≤35 weeks gestational age. Written pre-informed consent was taken from the parents. However, neonates with multiple anomalies incompatible with life, neonates who died within 7 days of birth and those where parental consent to participate was not given, were excluded.

Gestational age was decided by LMP-EDD, and if this was not reliable, then early trimester USG was considered. If no antenatal care was taken or no documents were available, then gestational age was estimated by the "new Ballard score"[16]. If any VLBW neonate who was part of the study showed signs of jaundice, a serum sample was obtained by heel prick and at the same time (+/-30miutes) TcB value was obtained by using Drager JM-103 transcutaneous bilirubinometer. Serum sample was processed in microlab's easybili-p instrument which measured serum bilirubin (TSB) by the spectrometric method using 450 nm and 570 nm wave length light. As all the neonates were preterm babies of ≤ 35 weeks, intervention was decided by the gestational age specific National Institute for Health and Care Excellence (NICE) guideline charts. Thereafter, serial monitoring of bilirubin was done by paired readings of TcB and TSB till 7 days of postnatal age. Maximum efforts were done to obtain TSB and TcB readings at the 24th hour of life (HOL), 48th HOL, 72nd HOL, 96th HOL, 120th HOL, 144th HOL and 168th HOL. A maximum of 30 minutes was tolerated between TSB and TcB. During phototherapy, an area over the sternum approximately double the size of JM-103 tip was covered with well thickened cotton swabs to keep the area unaffected by phototherapy. A total of 168 neonates were enrolled; however, 128 neonates were considered for statistical analysis as the rest did not have enough readings (<2) for analysis and in some neonates time lag between TcB and TSB was more than 30 minutes. Data analysis was carried out using MedCalc v-17.9.7. Correlation coefficient (r) and Bland Altman plot were done to check diagnostic accuracy of TcB value to TSB.

Results

A total of 128 neonates with gestational ages of ≤35 weeks and birthweights ≤1500g were included in the present study. These 128 neonates were subdivided into two groups i) ≤1000g (18 neonates) and ii) 1001-1500g (110 neonates). Gender and gestational age distribution are shown in Tables 1 and 2.

Table 1: ***Gender distribution of neonates (n=128)***

Birth weight (g)	Gender	Number of neonates
≤1000	Male	06
	Female	12
1001-1500	Male	53
	Female	57

Table 2: ***Gestational age distribution of neonates (n=128)***

Birth weight (g)	Gestational age (weeks)	Number of neonates
≤1000	28-30	11
	31	01
	32	02
	33	01
	34	03
	35	00
1001-1500	28-30	17
	31	15
	32	21
	33	27
	34	18
	35	12

Correlation co-efficient (r) value for subgroup i) total 146 and subgroup ii) total 857 paired data of TcB and TSB were collected and analysed and the r value was 0.87 and 0.89 respectively with the p value being <0.0001 suggesting statistically significant strong correlation (Table 3, Figure 1).

Table 3: ***Correlation coefficients (r) of subgroups***

Group	Observations	Number of paired data	'r' Value	p value
Subgroup i) Birthweight <1000g *n=18*	All the observations	146	0.87	<0.0001
	Before phototherapy	13	0.97	---
	After phototherapy	82	0.81	<0.0001
Subgroup ii) Birthweight 1001-1500g *n=110*	All the observations	857	0.89	<0.0001
	Before phototherapy	168	0.90	
	After phototherapy	529	0.83	

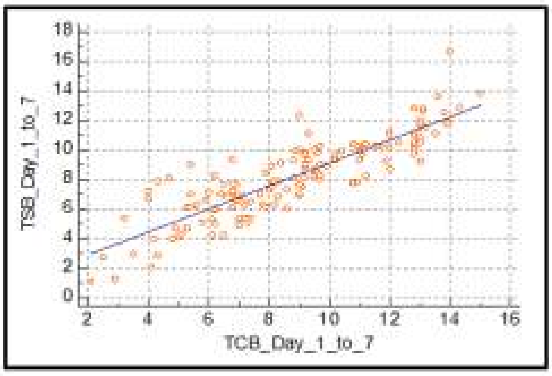

Figure1a: ***TCB-TSB scatter plot in babies <1000g birth weight showing strong positive correlation***

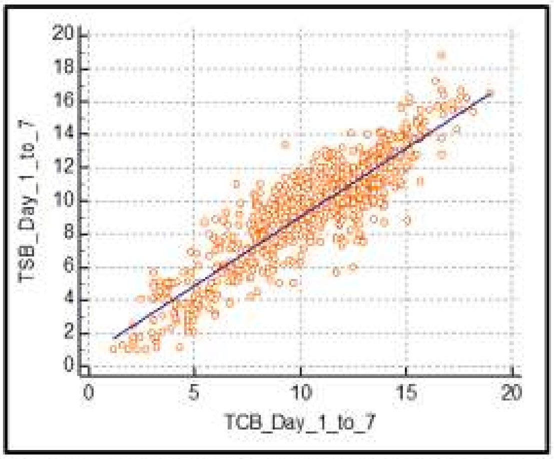

Figure1b: ***TCB-TSB scatter plot in babies, 1001-1500g birth weight showing strong positive correlation***

Data collected before starting phototherapy and after phototherapy were analysed separately for 13 neonates among subgroup i) and 101 neonates among subgroup ii). Correlation co-efficient r values for before phototherapy was 0.97 and 0.90 respectively for subgroup i) & ii) (Table 3, Figure 2).

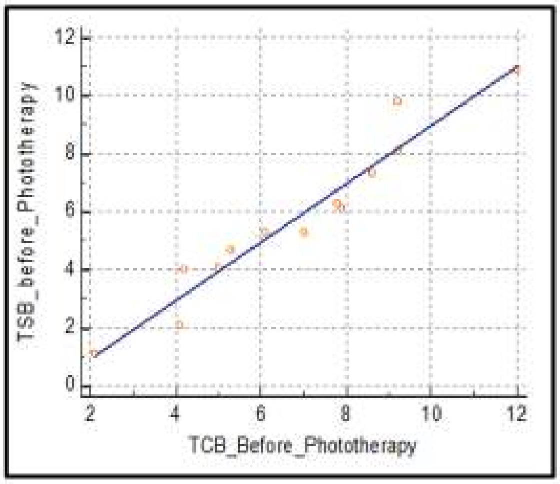

Figure2a: ***TCB-TSB scatter plot for readings before phototherapy in babies <1000g birth weight showing positive correlation. However, only 13 paired readings were obtained before phototherapy***

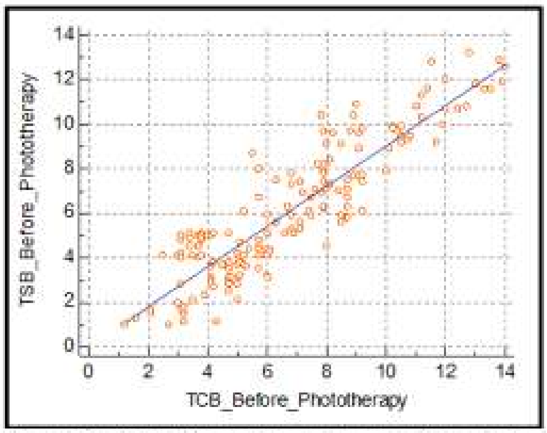

Figure2b: ***TCB-TSB scatter plot for readings before phototherapy in babies, 1001-1500g birth weight showing strong positive correlation***

However, for subgroup i) only 13 readings were available and hence more data are required to comment on statistical significance. Correlation co-efficient r values for after phototherapy were 0.81and 0.83, p value being <0.0001, for respectively for subgroup i) & ii) (Table 3, Figure 3). Hence TcB and TSB shows strong correlation in VLBW even after phototherapy.

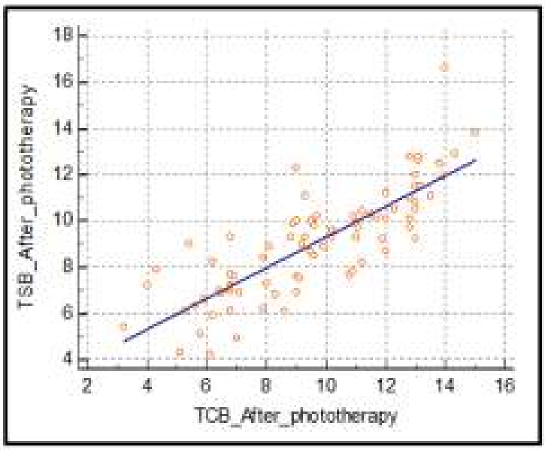

Figure3a: ***TCB-TSB scatter plot for readings after phototherapy in babies <1000g birth weight showing positive correlation***

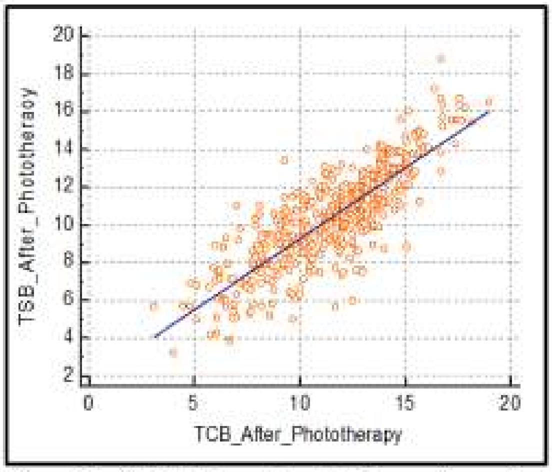

Figure3b: ***TCB-TSB scatter plot for readings after phototherapy in babies, 1001-1500g birth weight showing strong positive correlation***

As Pearson's correlation co-efficient is a poor indicator for agreement between two different methods of bilirubin estimation (i.e. TSB and TcB), we used Bland Altman Plot analysis. Figures 4 and 5 are the Bland-Altman plot analysis for subgroup-i) & subgroup-ii) respectively. These plots are suggestive of a statistically significant ($p<0.0001$) agreement between TcB and TSB in VLBW preterm neonates, and phototherapy does not affect the agreement.

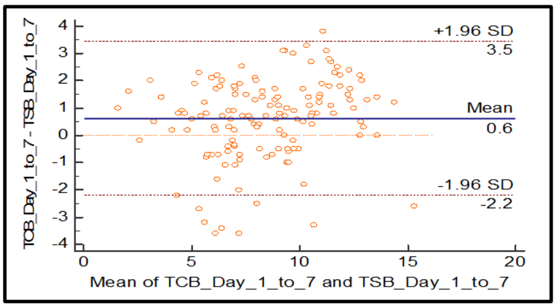

Figure 4a: ***Bland-Altman plot analysis for babies <1000g for all readings obtained throughout first 7 days of life. The difference of TcB and TSB was 0.63 mg/dl with SD 1.5 mg/dl at p-value <0.0001, Indicates TcB-TSB approximates each other significantly. Corresponding 95% limits were -2.2 mg/dl & +3.5 mg/dl respectively as shown in figure.***

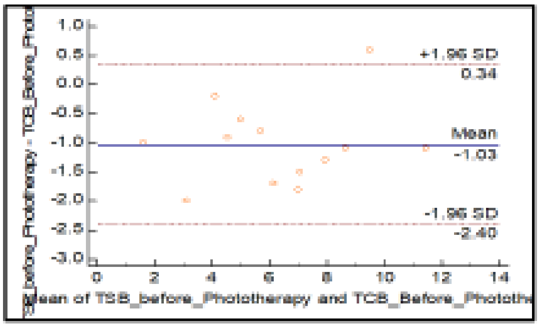

Figure 4b: ***Bland-Altman plotting for data of TcB and TSB before phototherapy in group of preterm birth weight ≤1000g. It is clear from the plot, mean of the difference is -1.03 ± 1.4 mg/dl. 95 % confidence interval is -2.4 mg/dl and +0.34 mg/dl. But there are only 13 paired data.***

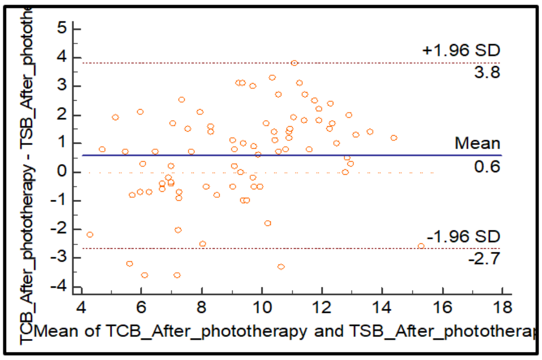

Figure 4c: ***Bland-Altman plotting for data of TcB and TSB after starting phototherapy in group of preterm birth weight ≤1000g. It is clear from the plot at p<0.0001 mean of the difference is 0.6±1.7 mg/dl. 95 % confidence interval is - 2.8 mg/dl and +3.8mg/dl, indicating there is strong agreement between TcB and TSB after the neonates gets exposed to phototherapy***

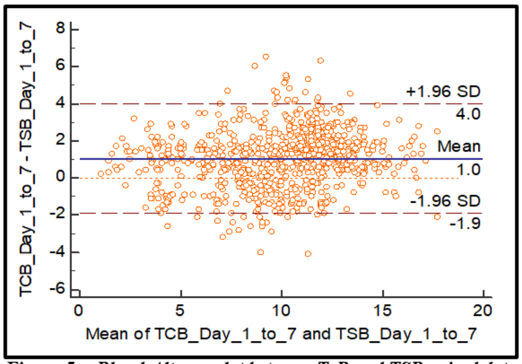

Figure 5a: ***Bland-Altman plot between TcB and TSB paired data of subgroup of neonates with birth weight >1000 to ≤1500g (n=110) from day 1 to 7 of postnatal age. Mean of the difference of TcB and TSB was 1.05 mg/dl with SD 1.5 mg/dl at p<0.0001, Indicates TcB approximates with TSB significantly. Corresponding 95% limits were -1.89 mg/dl & +3.99 mg/dl respectively as shown in the figure.***

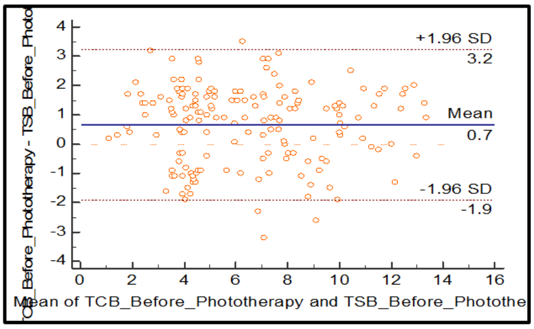

Figure 5b: ***Bland-Altman plotting for data of TcB and TSB before starting phototherapy in subgroup-ii (birth weight 1001 to 1500g). It is clear from the plot at p<0.0001 mean of the difference is 0.66±1.3 mg/dl again indicating TcB approximately equals TSB levels before starting phototherapy as mean of difference is near zero. Agreement interval at 95% is - 1.9 mg/dl and +3.2mg/dl, indicating there is stronger agreement between TcB and TSB before neonates gets phototherapy***

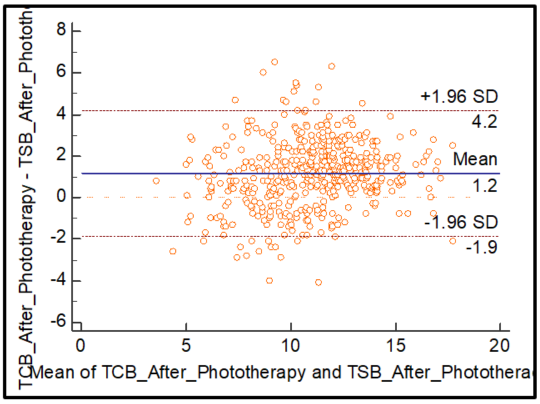

Figure 5c: ***Bland-Altman plotting for data of TcB and TSB after phototherapy in subgroup-ii (birth weight 1001-1500g). It is clear from plot at p<0.0001 mean of the difference is 1.16±1.5 mg/dl. Agreement interval at 95% is -1.86 mg/dl and +4.17mg/dl, indicating there is strong agreement between TcB and TSB after neonates get phototherapy.***

Discussion

The Drager Jaundice Meter-103 assesses yellowness of neonatal subcutaneous tissue by measurement of the difference between optical densities for light in the blue and green wavelength areas. As this optical density difference demonstrates a linear correlation with the SB concentration, it is converted into TSB and indicated digitally[18]. Advantages of this non-invasive technique are real-time results, cost-efficacy and avoidance of pain and local infection. Drager JM-103 TcB assessment can be used to identify the need for blood sampling for TSB levels in term and near-term neonate[2,18,19]. For the preterm infant current evidence is controversial. Several previous studies were done with various results and correlation coefficients ranged from 0.68 to 0.96[12,13,20].

In a study by Bhutani *et al*[1] there was a strong correlation between TcB and TSB in >2500g neonates. Negar *et al*[21] estimated r value which was 0.83 in >2500g neonates. However, r values estimated in VLBW neonates in 2009 by Karolayi *et al*[20], Sui ly *et al*[22], Stillova *et al*[23] suggest that there is strong correlation among VLBW neonates also. In our study we found that there is a strong correlation between TcB and TSB in VLBW neonates and this correlation is not affected even after phototherapy. In our study, we found that there is a statistically significant agreement between TcB and TSB in VLBW neonates as well and that phototherapy did not affect this agreement.

Conclusions

TcB measurements correlate significantly with TSB levels in early preterm neonates with VLBW. Phototherapy does not affect the correlation significantly.

References

1. Bhutani VK, Gourley GR, Adler S, Kreamer B, Dalin C, Johnson LH. Noninvasive measurement of total serum bilirubin in a multiracial predischarge newborn population to assess the risk of severe hyperbilirubinemia. *Pediatrics* 2000; **106**(2):E17. https://doi.org/10.1542/peds.106.2.e17 PMid: 10920173

2. Maisels MJ, Ostrea EM, Touch S, Clune SE, Cepeda E, Kring E, *et al.* Evaluation of a new transcutaneous bilirubinometer. *Pediatrics* 2004; **113**(6):1628–35. https://doi.org/10.1542/peds.113.6.1628 PMid: 15173483

3. Maisels MJ, Kring E, Rolinski B, Kreamer B, Dalin C, Johnson L. Transcutaneous bilirubinometry decreases the need for serum bilirubin measurements and saves money. *Pediatrics* 1997; **9**(4):599. https://doi.org/10.1542/peds.99.4.599 PMid: 9093305

4. Moyer VA, Ahn C, Sneed S. Accuracy of clinical judgment in neonatal jaundice. *Archives of Pediatrics and Adolescent Medicine* 2000; **154**(4):391–4.
https://doi.org/10.1001/archpedi.154.4.391
PMid: 10768679

5. Szabo P, Wolf M, Bucher HU, Haensse D, Fauchère JC, Arlettaz R. Assessment of jaundice in preterm neonates: comparison between clinical assessment, two transcutaneous bilirubinometers and serum bilirubin values. *Acta Paediatrica* 2004; **93**(11):1491–5.
https://doi.org/10.1111/j.16512227.2004.tb02635.x
PMid: 15513578

6. Anand KJS. Pain, plasticity, and premature birth: a prescription for permanent suffering? *Nature Medicine* 2000; **6**(9):971–3.
https://doi.org/10.1038/79658
PMid: 10973310

7. El-Beshbishi SN, Shattuck KE, Mohammad AA, Petersen JR. Hyperbilirubinemia and transcutaneous bilirubinometry. *Clinical Chemistry* 2009; **55**(7):1280–7.
https://doi.org/10.1373/clinchem.2008.121889
PMid: 19443565

8. Schmidt ET, Wheeler CA, Jackson GL, Engle WD. Evaluation of transcutaneous bilirubinometry in preterm neonates. *Journal of Perinatology* 2009; **29**(8):564–9.
https://doi.org/10.1038/jp.2009.38
PMid: 19322191

9. Kazmierczak SC, Robertson AF, Briley KP, Kreamer B, Gourley GR. Transcutaneous measurement of bilirubin in newborns: comparison with an automated Jendrassik-Grof procedure and HPLC. *Clinical Chemistry* 2004; **50**(2):433–5.
https://doi.org/10.1373/clinchem.2003.027326
PMid: 14752014

10. Rubaltelli FF, Gourley GR, Loskamp N, Modi N, Roth-Kleiner M, Sender A, *et al.* Transcutaneous bilirubin measurement: a multicenter evaluation of a new device. *Pediatrics* 2001; **107**(6):1264–71.
https://doi.org/10.1542/peds.107.6.1264
PMid: 11389241

11. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2004; **114**(1):297–316.
https://doi.org/10.1542/peds.114.1.297
PMid: 15231951

12. Nanjundaswamy S, Petrova A, Mehta R, Bernstein W, Hegyi T. The accuracy of transcutaneous bilirubin measurements in neonates: A correlation study. *Neonatology* 2004; **85**(1):21–5.
https://doi.org/10.1542/peds.114.1.297
PMid: 15231951

13. Namba F, Kitajima H. Utility of a new transcutaneous jaundice device with two optical path in premature infants. *Pediatrics International* 2007; **49**(4):497–501.
https://doi.org/10.1111/j.1442200X.2007.02386.x
PMid: 17587275

14. Knüpfer M, Pulzer F, Braun L, Heilmann A, Robel-Tillig E, Vogtmann C. Transcutaneous bilirubinometry in preterm infants. *Acta Paediatrica* 2001; **90**(8):899–903.
https://doi.org/10.1111/j.16512227.2001.tb02454.x
PMid: 11529539

15. De Luca D, Zecca E, de Turris P, Barbato G, Marras M, Romagnoli C. Using BiliCheck for preterm neonates in a sub-intensive unit: diagnostic usefulness and suitability. *Early Human Development* 2007; **83**(5):313–7.
https://doi.org/10.1016/j.earlhumdev.2006.06.006
PMid: 16949773

16. Limawal F, Madjid DA, Daud D. The accuracy of determining newborn's maturity between New Ballard's score, Ballard's score, and first day of last menstrual period. *Paediatrica Indonesia* 2008; **48**(2):59.
https://doi.org/10.14238/pi48.2.2008.59-63

17. Bland JM, Altman DG, Martin Bland J, Altman DG. Statistical methods for assesing agreement between two methods of clinical measurement. *Lancet* 1986; **1**(8476): 307-10. https://doi.org/10.1016/S01406736(86)90837-8

18. Yasuda S, Itoh S, Isobe K, Yonetani M, Nakamura H, Nakamura M, *et al.* New transcutaneous jaundice device with two optical paths. *Journal of Perinatal Medicine* 2003; **31**(1):81-8. https://doi.org/10.1515/JPM.2003.012 PMid: 12661149

19. Sanpavat S, Nuchprayoon I. Transcutaneous bilirubin in the pre-term infants. *Journal of the Medical Association of Thailand* 2007; **90**(9):1803–8.

20. Karolyi L, Pohlandt F, Muche R, Franz AR, Mihatsch WA. Transcutaneous bilirubinometry in very low birthweight infants. *Acta Paediatrica* 2004; **93**(7):941–4. https://doi.org/10.1111/j.16512227.2004.tb02693.x PMid: 15303810

21. Sajjadian N, Shajari H, Saalehi Z, Esphahani F, Taheri PA. ORIGINAL REPORT Transcutaneous bilirubin measurement in preterm neonates. *Acta Medica Iranica* 2012; **50**(11):765–70.

22. Siu LY, Siu LW, Au SK, Li KW, Tsui TK, Chang YY, *et al*. Evaluation of a transcutaneous bilirubinometer with two optical paths in Chinese preterm infants. *Hong Kong Journal of Paediatrics* 2010; **15**:132-40.

23. Stillova L, Matasova K, Zibolen M, Stilla J, Kolarovszka H. Transcutaneous bilirubinometry in preterm neonates. *Indian Pediatrics* 2009; **46**(5):405–8.