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Research Article

Comparison of Transcutaneous Bilirubin with Serum Bilirubin in Preterm Neonates before, during and after Phototherapy

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Abstract

Background: Objective:*To determine the diagnostic accuracy of transcutaneous bilirubin measurement for detecting hyperbilirubinaemia in preterm neonates.*

Study Design: *A prospective study .*

Place and Duration of Study: *The study was conducted at Dr. Sulaiman Alhabib Hospital, Rayyan, Riyadh, Saudi Arabia, which serves as a referral center for neonatal care in the region. The target population included all preterm neonates admitted to the NICUs during the 6 months study period from May to October 2024.*

Methodology:*The study included 199 preterm neonates admitted in our NICU during the designated 6 month study period and the data was entered into a statistical software package for analysis. Descriptive statistics were used to summarize the venous and transcutaneous bilirubin levels . Frequencies and percentages were reported for categorical variables, while means or medians with standard deviations were used for continuous variables, as appropriate.We analyzed the comparison between Transcutaneous and venous bilirubin levels in preterm neonates.Subgroup analysis was performed based on factors like gestational age and birth weight of the preterm Neonates.*

Resuts: *A total of 199 jaundiced preterm neonates were evaluated to asses the comparison between TCB and TSB values before,during and 12 hours after discontinuation of phototherapy. The mean difference between TSB and TCB was -16.00 (±19.643), which is statistically significant ($t = -11.491$, $p < .001$). During therapy, the difference sharply increased to 45.49 (±25.859) with an extremely significant t-value ($t = 24.817$, $p < .001$), highlighting that TSB values were higher than TCB.However, the high SD (25.859) again denotes variability in the two values, suggesting that not all neonates responded equally . After therapy, the difference dropped to 5.81 (±21.266), with a lower yet still significant $t = 3.853$, $p < .001$. This reflects that although TSB values were still higher than TCB but the difference was much smaller as compared to during phototherapy and thus TCB can be used as a gold standard for monitoring jaundice in these neonates.*

Conclusion: *In our study we noted a significant positive correlation between TCB and TSB in preterm neonates who required phototherapy for hyperbilirubinemia before during and after phototherapy especially in extreme preterms.*

Key words: *Transcutaneous bilirubin, Serum Bilirubin, Hyperbilirubinemia, Preterm Neonates, Gestationl age, Birth weight*

Introduction

Neonatal jaundice is one of the most common cause of hospital admission during the first week after birth and occurs due to hyperbilirubinemia (1,2)). Most cases are benign, but severe neonatal hyperbilirubinemia can result in bilirubin encephalopathy/ kernicterus(3). Severe Neonatal hyperbilirubinemia and its sequelae can be prevented with appropriate serum bilirubin monitoring and early treatment involving phototherapy or exchange blood transfusion.(4,5). Although the American Academy of Pediatrics recommends universal screening of all babies for neonatal jaundice, it seems impractical in developing countries with limited resources.(6,7) In the first week following birth, 60% of term and 80% of preterm neonates experience clinical jaundice (9). Physiological jaundice appears within the first 24 hours of birth and can disappear on its own or may increase in intensity but mostly it has a benign course.. Pathological jaundice, on the other hand, develops during the first 24 h of life, according to estimations, 1.1 million babies worldwide may have severe hyperbilirubinemia each year, mostly occurring in Sub-Saharan Africa and South Asia .Severe neonatal jaundice affects around 481,000 late-preterm and term newborn newborns worldwide every year, resulting in 114,000 deaths and over 63,000 survivors with significant morbidity and long-term disabilities.(8)

Unconjugated hyperbilirubinemia is the more common type and can be either physiological or pathological. Physiological jaundice accounts for 75% of neonatal hyperbilirubinemia and results from a physiological alteration in neonatal bilirubin metabolism. Healthy adults have a normal TSB level of less than 1mg/dl in contrast to neonates, where TSB levels are physiologically higher. Even in healthy full-term newborns, there is an increased bilirubin load owing to increased red blood cells (RBC) mass and a decreased RBC lifespan. Clearance of bilirubin from the blood is also compromised in neonates due to impaired activity of uridine diphosphate countertransference (UGT), the enzyme needed for bilirubin conjugation.(9,10) Moreover, these neonates also have increased enterohepatic circulation which is either due to exclusive breast feeding causing dehydration, or from reduced intestinal bacteria that usually convert bilirubin to nonresorbed metabolites, further contributing to elevated TSB levels. Physiological jaundice typically appears after 24 hours of age, peaks at around 48-96 hours, and resolves by two to three weeks in full-term infants.(11)

Jaundice is considered to be pathological if it appears on the first day of life, Serum bilirubin is more than the 95th centile for age based on age-specific bilirubin nomograms, levels rise by more than 5 mg/dL/day or more than 0.2 mg/dL/hour, or jaundice persists beyond 2 to 3 weeks in full-term neonates.(10) .

Wether jaundice is physiological or pathological,it is basically caused by any of the three mecahnisms ,bilirubin overproduction,decreased bilirubin conjugation or impaired excretion and can result in significant morbidity and even mortality in neoantes if not managed properly,raising the need for accurate and frequent monitoring of jaundice in neonates(12).

TSB measurement is still considered the gold standard. But it is invasive, painful and costly in terms of workload, time and money. Moreover, there is a concern of significant blood loss due to repeated sampling especially in preterms. TCB being a noninvasive method can overcome these problems(7,8). Studies have shown good correlation between TSB and TCB in various ethnic groups by various authors(6)

Methodology

This Prospective Study was conducted for 6 months from June to November 2024 at Neonatal Intensive Care Unit in Rayyan Hospital at Dr Sulaiman Al Habib Hospital Riyadh ,Saudi Arabia,after approval from the hospital Ethical Review Committee(RC24.06.03).An Informed consent of parents was taken before enrolling them in the study.The 199 Preterm neonates having unconjugated hyperbilirubinemia irrespective of aetiology and requiring phototherapy according to American Academy of pediatrics (AAP) nomogram charts were kept naked with only diaper and eye cover to allow maximum skin exposure to phototherapy(13).Phototherapy was given using ZEAL- LED standard phototherapy units which emit a wavelength of 400-550 nm.Phototherapy was interrupted only during feeding breaks and it wa stopped once 2 readings were recorded below the threshold of phototherapy on the standard Phototherapy charts used in our NICU.All neonates in the study underwent intravenous blood sampling for TSB through fully automated spectrophotometer and TCB readings were obtained from the forehead covered by eye pads with the help of a latest version of Drager JM-105.All TSB readings were taken before ,during and after 12 hours of discontinuation of phototherapy.TCB readings (average of 3 readings at forehead) were taken within 15 minutes of extracting TSB samples.

Sample Size and Data Analysis:

A priori sample size of 199 infants was calculated using G power (version 3.1.9.4) to determine the difference between TcB and TSB using phototherapy with a p value of 0.05 by adjusting statistical power up to 80% to ensure an adequate probability of detecting a true effect. This study completed its statistical evaluation using Statistical Package for Social Sciences (SPSS) version 22.0. The quantitative variables were presented as Mean ± Standard Deviation (SD), whereas categorical variables were expressed in frequencies and percentages. A paired sample t-test was employed to evaluate and compare the differences in mean values of total serum bilirubin (TSB) and transcutaneous bilirubin (TcB) at three different stages (before, during, and after therapy respectively). Moreover, subgroup analyses were also performed based on gender, gestational age and birth weight parameters. The 95% Confidence Interval (CI) for the mean difference was also reported for each comparison to indicate the precision of the estimates. A p-value less than or equal to 0.05 was considered statistically significant throughout the analysis.

Inclusion criteria

1-All pre-term neonates less than 37 weeks gestation with clinical diagnosis of Neonatal jaundice and requring phototherapy for the first time in first 7 days of life.The gestational age of neonates was confirmed by date of last menstrual period or first trimster scan and cofirmed by Ballard scoring.

Exclusion criteria:

1-All full term neonates more than 37 weeks gestation with Neonatal jaundice.

2-Parental denial of consent to be included in the study group

3-sick preterm newborns requiring intensive care

4-Preterm neonates who underwent phototherapy before

5-Neonates who required exchange transfusion

Results

A total of 199 jaundiced preterm neonates were evaluated to asses the comparison between TCB and TSB values before,during and 12 hours after discontinuation of phototherapy . Table 1 illustrates the overall dataset which shows bilirubin levels across the therapy timeline. Before therapy, the mean difference between Total Serum Bilirubin (TSB) and Trans cutaneous Bilirubin (TCB) was -16.00 mg/dl (±19.643), which is statistically significant ($t = -11.491$, $p < .001$). The negative mean suggests that TCB values were considerably higher than TSB, reflecting higher concentrations of bilirubin detected by Drager JM-105 in the skin prior to phototherapy. During therapy, the difference sharply increased to 45.49 mg/dl (±25.859) with an extremely significant t-value ($t = 24.817$, $p < .001$), highlighting that TSB values were higher than TCB.However, the high SD (25.859) again denotes variability in the two values, suggesting that not all neonates responded equally . After therapy, the difference dropped to 5.81mg/dl (±21.266), with a lower yet still significant t = 3.853, p < .001. This reflects that although TSB values were still higher than TCB but the difference was much smaller as compared to during phototherapy. The overall trend indicates the efficacy of TCB especially before and after phototherapy and also to some extent during phototherapy in these vulnerable preterm neonates.

Table 1

Conditions	N	Difference (TSB - TCB) (Mean ± SD)	t-value	p-value	95% CI for Mean Difference	
					Lower	Upper
Before Therapy	199	-16.00 ± 19.643	-11.491	.000	-18.746	-13.254
During Therapy		45.49 ± 25.859	24.817	.000	41.878	49.107
After Therapy		5.81 ± 21.266	3.853	.000	2.836	8.782

Table 2 presents sub-group analysis when stratified by gender, both males and females demonstrated similar agreement between TCB and TSB; however, subtle distinctions were noteworthy. For male neonates, the pre-phottherapy difference was-15.29 (±20.565) (t = -7.725, p < .001), while during therapy, it rose to 46.17 (±26.837) (t = 17.877, p < .001), and post-therapy, it dropped to 5.43 (±22.216) (t = 2.538, p = .013). The smaller post-phototherapy t-value and p-value nearing 0.01 indicate a relatively weaker agreement between TCB and TSB values , potentially due to physiological differences likely higher baseline bilirubin levels in male neonates.

In contrast, female neonates showed a pre-therapy difference of -16.85 (±18.566) (t = -8.656, p < .001), during therapy 44.69 (±24.771) (t = 17.211, p < .001), and after therapy 6.26 (±20.193) (t = 2.959, p = .004). The slightly higher post-therapy t-value and lower p-value suggest a more sustained agreement between TCB and TSB in females. While the comparson is effective in both genders, females appear to show similar TCB and TSB levels post-phtotherapy. This could reflect sex-based differences in skin maturation or hormonal factors influencing bilirubin metabolism.

Table-2

Conditions	Gender	N	Difference (TSB - TCB) (Mean ± SD)	t-value	p-value	95% CI for Mean Difference	
						Lower	Upper
Before Therapy	**Male**	108	-15.29 ± 20.565	-7.725	.000	-19.210	-11.364

During Therapy			46.17 ± 26.837	17.877	.000	41.047	51.286
After Therapy			5.43 ± 22.216	2.538	.013	1.188	9.664
Before Therapy	**Female**	91	-16.85 ± 18.566	-8.656	.000	-20.713	-12.980
During Therapy			44.69 ± 24.771	17.211	.000	39.533	49.851
After Therapy			6.26 ± 20.193	2.959	.004	2.058	10.469

Table 3 sub-group analysis offers critical insights into how gestational maturity impacts on agreement between TCB and TSB values.. Extreme preterm infants (GA ≤ 28 weeks) had a pre-therapy difference of -21.58 (±9.112) (t = -10.322, p < .001), indicating higher TCB values than TSB . During therapy, the difference increased to 7.21 (±7.254) (t = 4.333, p < .001), reflecting still some modest agreement between TCB and TSB. However, after phototherapy, the difference was 3.95 (±11.123) with a non-significant t = 1.547 (p = .139). This non-significance also suggests much better agreement between TCB and TSB in extreme preterms. Conversely, moderate-to-late preterm infants (GA > 28 weeks) showed a pre-therapy mean of -15.41 (±20.366) (t = -10.152, p < .001), during therapy increase to 49.57 (±23.776) (t = 27.893, p < .001), and post-therapy value of 6.01 (±22.077) (t = 3.650, p < .001). The strong significance throughout indicates better agreement between TCB and TSB values before and after phototherapy likely due to more mature hepatic systems and better phototherapy response .However extreme preterms show a stronger agreement between TCB and TSB before ,during and after phototherapy.

Table- 3

Conditions	**GA**	**N**	**Difference (TSB - TCB) (Mean ± SD)**	**t-value**	**p-value**	**95% CI for Mean Difference**	
						Lower	**Upper**
Before Therapy	**Ex-Pre-term (GA ≤ 28 weeks)**	19	-21.58 ± 9.112	-10.322	.000	-25.971	-17.187
During Therapy			7.21 ± 7.254	4.333	.000	3.714	10.707
After Therapy			3.95 ± 11.123	1.547	.139	-1.414	9.308
Before Therapy	**Pre-term (GA > 28 weeks)**	180	-15.41 ± 20.366	-10.152	.000	-18.407	-12.416
During Therapy			49.57 ± 23.776	27.893	.000	46.063	53.077
After Therapy			6.01 ± 22.077	3.650	.000	2.758	9.253

Table 4 presents sub-group on basis of birth weight.Low birth weight neonates (≤1500g) had a pre-therapy difference of -15.49 (±23.832) (t = -4.550, p < .001), which is clinically significant but less robust statistically compared to higher BW infants. During therapy, the mean difference rose again to 22.65 (±25.658) (t = 6.180, p < .001), and post-therapy settled at 6.18 (±15.496) (t = 2.793, p = .007). The moderate t-values and large standard deviations imply a somewhat inconsistent agreement , possibly due to underlying factors like thin skin and low body fat to muscle ratio.On the other hand, neonates >1500g demonstrated stronger and more consistent responses. Pre-therapy mean difference was -16.17 (±18.156) (t = -10.905, p < .001), phototherapy-phase mean soared to 52.95 (±21.188) (t = 30.609, p < .001), and post-therapy value was 5.69 (±22.881) (t = 3.044, p = .003). These figures again reflect high agreement between TCB and TSB before and after phototherapy but comparatively higher TSB values than TCB during phototherapy , with a particularly striking t-value during therapy but still with significant P-value highlighting the fact that TCB can be considered as an important monitoring tool especially in peterm neonates with comparatively good birth weights.

Table-4

Conditions	BW	N	Difference (TSB - TCB) (Mean ± SD)	t-value	p-value	95% CI for Mean Difference	
						Lower	Upper
Before Therapy	**(BW ≤ 1500)**	49	-15.49 ± 23.832	-4.550	.000	-22.335	-8.644
During Therapy			22.65 ± 25.658	6.180	.000	15.283	30.023
After Therapy			6.18 ± 15.496	2.793	.007	1.733	10.635
Before Therapy	**(BW > 1500)**	150	-16.17 ± 18.156	-10.905	.000	-19.096	-13.237
During Therapy			52.95 ± 21.188	30.609	.000	49.535	56.372
After Therapy			5.69 ± 22.881	3.044	.003	1.995	9.378

Discussion

In the present study all the 199 preterm neonates who underwent phototherapy demonstrated a strong correlation between TSB and TcB levels before and after phototherapy values but this correlation became weaker with exposure to phototherapy most likely due to the bleaching effect of the skin but the correlation persisted in extreme preterm neonates. So, the TcB can be used as an initial screening and monitoring tool for preterm neonates.

The strongest correlation between TcB and TSB was found before starting the phototherapy in our study. The correlation coefficients we calculated were almost similar to those reported by others(14,15,16,17) For neonates under phototherapy, the correlation between the TcB value and TSB was stronger in extreme preterms. Of the total 199 preterm 19 were extreme peterms ,2 were 24 weeks,7 nonates 25 weeks,4 were 26 weeks,2 were 27 weeks and 4 were 28 weeks.Our study highlighted the importance of TCB monitoring in this vulnerable age group before ,during and after phototherapy similar to the results of the study conducted by Sahota R et al,which showed strong agreement between TCB and TSB in this vulnerable age group thus avoiding excessive sampling and handling(18)Also Nagar G et al. showed that TcB could reliably estimate TSB in preterm neonates less than 32 weeks of gestation(19).This result is in contrast to the results of study conducted by Kumar.D and Kumar.D which showed significant similarity between TCB and TSB only before and after phototherapy(20). we also demonstrated that there was a good correlation and high consistency between TcB and TSB 12 hours after discontinuation of phototherapy in all preterm neonates including those less than 28 weeks gestational age with jaundice.This result was similar to the results of the study by Sahota R et al (18) but in contrast to the study conducted by Yang S.T et al who showed more correlation in term and late preterm neonates only.(21)

Some studies mentioned that bilicheck has a tendency to overestimate serum bilirubin(15,22); whereas others mentioned that the TcB level measured using BiliChek was on average lower than the TSB level.(23) In our study, we found that the mean TcB level is mostly higher than the mean TSB level in all preterm neoantes before photothearapy and in extreme preterm neonates during phototherapy and is somewhat similar to TSB in all preterm neoanates 12 hours after phototherapy.

Moreover no significant correlation was found between the differences between TcB and TSB and the associated factors including birth weight, sex, or the intensity of phototherapy, comparable to the findings of Taylor et al. who reported that the differences between TcB and TSB were not significantly associated with gender or birth weight.(24)

There are several limitations in our study. First,the sample size was small.Secondly we did not measure TcB on different sites simultaneously. We only measured the TcB level in the skin of the middle forehead which was covered by eye pads, thus, the correlation between TcB and TSB at other anatomic sites is unknown in the our study as there are contrasting results regarding TcB measurement on different sites. Kurokawa et al. mentioned that the accuracy of TcB measurements varies according to the body site of very low birthweight Japanese infants, and TcB on the sternum is more reliable than that on the forehead.(25) However, Nagar G et al. found that TcB on the forehead had a slightly better correlation than that on the sternum or other sites.(19). Rubaltelli et al.also mentioned that the forehead TcB determination was more comparable to TSB than the sternum TcB determination.(26) .Also Ho S.R also recommended forehead as the preferable site of TCB measurement and that it had strong correlation with the corresponding TSB levels which is in agreement with our study.(27)

The main strength of our study is that we compared TCB and TSB measurements in preterms including extreme preterms ,moreover our study indicated a more convenient skin site (forehead) .Our findings could help clinical practitioners better judge and avoid underestimating the transcutaneous bilirubin level.

Recommendations

All preterm Neonates should be screened at birth with Transcutaneous bilirubin measured by bilirubinometer Drager JM 105 and later on if they develop jaundice and require phototherapy ,monitoring should be continued with TCB monitoring especially before and after photherapy and even during phototherapy in extreme preterms who are less than 28 weeks and have birth weight less than 1500 gms, in order to minimize the effect of excesive blood sampling on these vulnerable preterm neonates.

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Conclusion

In our study we noted a significant positive correlation between TCB and TSB in preterm neonates who required phototherapy for hyperbilirubinemia before and after phototherapy and in extreme preterms with birth weight less than 1500 gms and gestational age of less than 28 weeks also had good agreement even during phototherapy . Hence, in future, TSB measurements can be replaced by TCB measurements for monitoring bilirubin levels in neonates suffering from hyperbilirubinemia, as TCB measurement is a reliable, noninvasive method and uses less resources.

Conflict of Interest: None.

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