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Local Experience of Transcutaneous Bilirubinometry – An Accurate Alternative to Serum Sampling?

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BACKGROUND

Babies are frequently referred to the Paediatric Emergency Department from the Breastfeeding Clinic and Community Discharge Liaison Service with jaundice, as indicated by high transcutaneous bilirubin (TCB) readings measured using transcutaneous bilirubinometry. Serum bilirubin (SeB) testing is then performed in the Emergency Department and the decision for admission for phototherapy is based upon on the SeB. Strict correlation between these modes of bilirubin measurement would negate the need to verify TCB with SeB in cases where the bilirubin level is clearly above the cut–off value, thus reducing hospital waiting time, costs and time to starting treatment.

OBJECTIVES

To establish whether TCB is a reliable screening test for neonatal jaundice that may require phototherapy based on the relationship between TCB and SeB levels in patients in Malta.

METHOD

Neonates referred from the Breastfeeding Clinic to the Paediatric Emergency Department with raised TCB levels over five months (June-October 2017) were included. Data was obtained from the Breastfeeding Clinic, local delivery suite and iSOFT Clinical Database, and interpreted using in-built data analysis tools and custom-made data analysis spreadsheets on Microsoft Excel®.

RESULTS

There was a significant difference between the two groups, with mean TCB being significantly greater than SeB (t=2.32, p=0.04), in fact TCB was greater than SeB in 18 out of 24 neonates. However, TCB occasionally also under-read bilirubin levels.

CONCLUSIONS

These findings differ from results of similar studies conducted in other centres. Given the significant difference between TCB and SeB, it is recommended that, locally, TCB values continue to be cross-checked with SeB levels in the Emergency Department prior to establishing the need for phototherapy in neonatal jaundice.

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Introduction

Neonatal jaundice is common, occurring in over 50% of term neonates and over 80% of pre-terms.[1] Jaundice is the result of hyperbilirubinaemia, due to excess red blood cell breakdown or decreased excretion. It may be visually gauged, by looking for yellow discolouration at certain body sites such as the sclerae and the skin. However, this clinical method of detecting hyperbilirubinemia is subjective and should ideally be confirmed biochemically.[2]

In many cases, neonatal jaundice is transient and resolves spontaneously. However, in others hyperbilirubinaemia may be a significant cause of morbidity and mortality, with neurological complications such as hearing loss, kernicterus leading to cerebral palsy, and a mortality of 7-10%.[1-2] The aim of treatment is to reduce bilirubin levels before such complications occur.[3]

Bilirubinometers used to consist of 2-wavelength devices, i.e. 460nm and 520 nm, in order to generate a jaundice index. This method, however, required that a baseline bilirubin measurement be known.[3] Newer bilirubinometers, including those currently used locally (Philips BiliCheck®), utilise the entire visible spectrum (380 nm -760 nm) and have the advantage of not being affected by variables such as infant age, gestation or ethnicity, and do not require a baseline bilirubin level.[3]

Locally, babies are frequently referred to the Paediatric Emergency Department from the Breastfeeding Clinic and the Community Discharge Liaison Service because of high transcutaneous bilirubinometry (TCB) readings. Readings are obtained by applying the device to the sternum or forehead of the neonate. Elevated bilirubin levels are then verified in the Emergency Department using serum bilirubin (SeB) levels and the need for admission for phototherapy based on the latter.

This study was carried out to examine the association between TCB and SeB. A close association would negate the need for unnecessary venupuncture and would decrease the time from first medical contact to starting phototherapy, in patients in whom TCB levels are clearly elevated above accepted cut-off levels. Furthermore, it would also decrease hospital costs associated with SeB sampling and analysis.

Method

This study was conducted at Mater Dei Hospital, Malta, the country's main hospital (928 in-patient and 86 day-care beds).[4] It included all neonates referred from the local Breastfeeding Clinic to the Paediatric Emergency Department with neonatal jaundice as indicated by a raised TCB level, measured using *Philips® BiliChek* monitoring device, over a five month period (June-October 2017). Data from this cohort was obtained directly from the Breastfeeding Clinic, with information regarding gestational age obtained from the local delivery suite in patients in whom this had not been documented by the Breastfeeding Clinic.

SeB was obtained from iSOFT Clinical Database for the remaining 24 neonates, the lab test used being the 'total bilirubin level' (BILT3 Cobas®).

Statistical Analysis

Data was subsequently interpreted using data analysis tools in Microsoft Excel and custom-made spreadsheets with data analysis functions.

A contingency table was drawn up to determine the use of TCB as a screening test for SeB, based on whether or not phototherapy as predicted by TCB was actually required at respective SeB values, and data interpreted from this table to look at positive and negative predictive values of TCB.

TCB results >350 μmol L^{-1} were also analysed separately from TCB <350 μmol L^{-1} due to the fact that values >350 μmol L^{-1} encompassed all readings above 350 μmol $L^{-1}$and could not be translated as a simple numerical figure for interpretation. Statistics were calculated for the 14 TCB values <350 μmol L^{-1} and their respective SEB values, with a paired t-test to assess relationship. Of the TCB values <350μmol L^{-1} the differences between TCB and respective SeB were calculated and statistics for these differences obtained, looking at under- and over-reading by the device.

The following were exclusion criteria for our study:

- Babies referred from the Breastfeeding Clinic to the Paediatric Emergency Department for jaundice on dates outside the study period
- Neonates born at <35 weeks gestational age
- Measurements before one day of age (before first 24 hours)

Results

During the study-period, we looked at 25 neonates referred from the breastfeeding clinic in view of raised TCB levels, however, one was excluded from data interpretation in view of TCB level not having been documented prior to referral to Emergency Department. Results wherein TCB was indicated as >350 μmol L^{-1} were analysed separately. For those <350 μmol L^{-1}, summary statistics for the two groups are shown in table 1.

Table 1 Summary Statistics for TCB and SeB values in patients with TCB <350 μmol L^{-1}, showing 95% lower confidence intervals (LCI) and upper confidence intervals (UCI)

Results		LCI (95%)	UCI (95%)
Sensitivity	94.7%	71.9%	99.7%
Specificity	40.0%	7.3%	83.0%
Positive predictive value	85.7%	62.6%	96.2%
Negative predictive value	66.7%	12.5%	98.2%
Accuracy	83.3%	61.8%	94.5%
Relative risk	2.6		
Odd's ratio	12.0		

There was a significant difference between the two groups in that mean TCB was significantly greater than SeB (t=2.32, *p*=0.04), as shown in table 2 which gives the values for the t-test employed in this study.

Table 2 Paired t-test for TCB and SeB values in patients with TCB <350 μmol L^{-1}

	TC	*SeB*
Mean	306.2143	288.5214
Variance	578.6429	1178.482
Observations	14	14
Pearson Correlation	0.572894	
Hypothesized Mean Difference	0	
Df	13	
t Stat	2.32469	
P(T<=t) one-tail	0.018463	
t Critical one-tail	1.770933	
P(T<=t) two-tail	0.036926	
t Critical two-tail	2.160369	

However, TCB occasionally also under-read bilirubin levels, and the differences are summarised in table 3 which compares the extent at of under- and over-reading of TCB.

Table 3 Extent of under- and over-reading for TCB

	Under	Over
Mean	-17.4	31.7
Median	-17.8	33.7
Standard Deviation	10.4	19.2
Min	-29.6	2.4
Max	-4.6	67.7
N	4	10
Confidence interval	16.5	13.7

Table 4 Further statistics for TCB and SeB values in patients with TCB <350 μmol L^{-1}

	TC	Serum
Mean	306.2	288.5
Median	306.5	286.9
Standard Deviation	24.1	34.3
Min	274.0	230.3
Max	340.0	350.1
Confidence interval	13.9	19.8

Table 5 Contingency table indicating whether or not phototherapy was required based on values for TCB and SeB according to age-appropriate charts

	SeB Yes	SeB No
TCB Yes	18	3
TCB No	1	2

In fact, considering all neonates investigated, TCB levels were definitely greater than SeB in 18 cases, however, in two cases where both TCB and SeB were >350 we were unable to determine which was actually higher. In four cases TCB values were lower than SeB. Note that in stating that TCB over- or under-read results, we assume that SeB is the gold-standard method for analysing bilirubin levels.

Further statistics for TCB and SeB values <350 μmol L^{-1} are seen in table 4, and the contingency table used to work out summary statistics is seen in table 5.

TCB, as a screening test for the need for phototherapy in the setting of neonatal jaundice, while sensitive (sensitivity=94.7%) was poorly specific (specificity=40.0%). In fact despite a positive predictive value of 85.7%, this method of gauging bilirubin levels has a negative predictive value of only 66.7%.

Discussion

Contrary to results from similar studies conducted in other centres, there was a significant difference between the two groups in this study in that mean TCB was significantly greater than SeB. Of note is a study performed by the Medical University of South Carolina in the USA, published in 2015.[2] Here, the same bilirubinometer make was identical to that used in this study. Srinivas *et al.* report that given the good correlation between TCB and SEB in their study, TCB could reliably be used as a stand-alone screening test for neonatal jaundice.

The accuracy of TCB as a screening test for SeB was validated in many in-patient studies, with a correlation between BiliCheck® and high pressure liquid chromatography of 0.89 in one large, multicentre, hospital-based study. [3] Wickremasinghe et al (2011) noted a

decreased sensitivity and specificity of TCB in relation to SeB in an out-patient setting, with a tendency towards over-reading, and this was attributed to an increase in the incidence of hyperbilirubinaemia following hospital discharge, decreased moisture of neonatal skin and pigmentary differences.[5] This tendency of TCB to over-read SeB is similar to that seen in this study. Furthermore, Maisels *et al.,* (2011) noted an increase in false negatives picked up by TCB with increasing TCB levels.[6] Other out-patient based studies have shown a good correlation between TCB and SeB.[7]

This study shows that TCB is not a reliable screening test for SeB. Although our study showed a statistical difference between TCB and SeB ($t=2.32$, $P=0.04$), the limitations of our study include the following:

a. Since TCB measurement was unwitnessed, the method of device use might have been suboptimal in some instances
b. This study relied on TCB results collected by third-parties, however, although to our knowledge the majority of TCB levels of babies referred to the Paediatric Emergency Department in view of neonatal jaundice was documented, there might have been instances were no such record was kept, and the extent of under-documentation might have varied from individual to individual, with some midwives documenting results much more than others. This should not have been an issue if there were no differences in TCB measurement technique by different midwives and if each midwife had the same threshold for TCB measurement with a bilirubinometer.
c. Our data pool was small and the population size might have negatively affected reliability of results.
d. The results obtained are relevant for the bilirubinometer used in our study. These may or may not be able be applicable to other bilirubinometers
e. The following assumptions were made in our study, and these too might have affected results:
    - Transcutaenous bilirubinometry accuracy is independent of other variables including race, gestational age, post-natal age, general health and nutrition status
    - Values on transcutaneous bilirubinometry are independent of site of measurement
    - The transcutaneous bilirubinometer was adequately calibrated and functioning well
    - Proper technique was used in obtaining transcutaneous bilirubin readings
    - Transcutaneous and serum bilirubin readings were done in close chronological proximity, i.e. the time lag between transcutaneous bilirubinometer and serum sampling was not significant enough to affect results
    - Serum samples were kept in similar conditions until analysed in the laboratory, including avoiding exposure to sunlight
    - The serum test done locally is reliable and provides a true value for serum bilirubin

Conclusion

Given the significant difference between TCB and SeB in our study, it is recommended that,

locally, baseline SeB levels continue to be checked prior to deciding on the need for phototherapy in neonatal jaundice unless a larger study concludes otherwise. It would be worth repeating this study at a later date using a larger cohort of patients, to conclude whether the results seen in our study were truly reliable, or whether they were seen by chance given the confounding factors of our study.

Summary

The facts:

1. In Malta, patients are routinely referred from the breastfeeding clinic in view of elevated TCB
2. TCB gives a quick indication of SEB
3. TCB and SEB values are well-comparable according to previous studies
4. Using TCB values alone decreases on hospital waiting time and decreases time to start of treatment in hyperbilirubinaemia

What's new?

1. TCB does not appear to be a sensitive enough indicator of SEB in our local cohort
2. TCB over- and sometimes under-estimates SEB
3. TCB results as indicated from breastfeeding clinic referrals should continue to be verified with SEB in our local cohort to decide on treatment, unless a larger study proves otherwise

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