Simultaneous measurement of total transcutaneous bilirubin on forehead and chest as a predictive model for total serum bilirubin in premature and term newborns

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ABSTRACT

Background: detection of hyperbilirubinemia in neonates has become a challenge for healthcare systems. The objective of this study was to determine the usefulness of simultaneous measurements of total transcutaneous bilirubin on forehead (TTBf) and total transcutaneous bilirubin on chest (TTBs) as a predictive model for total serum bilirubin (TSB) in premature and term neonates.

Material and methods: a transverse and analytical study in neonates with gestational age between 30 and 42 weeks, from January 21 through April 30, 2013, at a public gynecology, obstetrics, and neonatology hospital. Pearson correlation was determined between TSB/TTBf and TSB/TTBs. Linear regression analyses were conducted for one and for several independent variables.

Results: for 89 simultaneous determinations the correlation between TSB/TTBf was 0.8411 and for TSB/TTBs 0.7942 ($p < 2.2$ E-16 for both cases). With the simple regression analysis between TSB and TTBf the equation was: TSB $= 2.1187 + 0.7035 \times$ TTBf ($p < 2.2$ E-16, $R^2 = 70.75\%$, $R^2_{adjusted} = 70.41\%$); for TSB and TTBs the equation was: TSB $= 2.0405 + 0.6349 \times$ TTBs ($p < 2.2$ E-16, $R^2 = 63.07\%$, $R^2_{adjusted} = 62.65\%$). With multiple regression analysis for TSB vs. TTBf, TTBs the equation was: TSB $= 1.620 + 0.503 \times$ TTBf $+ 0.224 \times$ TTBs ($p < 2.2$ E-16, $R^2 = 72.87\%$, $R^2_{adjusted} = 72.24\%$).

Conclusions: it was proven that the model that included TTBf and TTBs allowed us to obtain a better prediction of TSB than models with a single measurement of TTB in hospitalized premature and term neonates.

Key words: transcutaneous bilirubin, bilirubinometer, neonatal hyperbilirubinemia, kernicterus.

One of the strategies implemented by healthcare systems, seeking to lower the incidence of different subtypes of kernicterus in newborns, is early detection of hyperbilirubinemia. Identification of neonates at risk is complicated, among other factors, by the fact that hospital release occurs before bilirubin levels have reached their maximum peak. The reference method for measuring bilirubin has been quantification in serum; however, the American Academy of Pediatrics, in its Clinical Practice Guidelines for management of hyperbilirubinemia in newborns of 35 weeks or more,[1,2] recommends screening bilirubin, either serum or transcutaneous. The latter offer some advantages: they avoid painful punctures and blood loss for the neonate, results are obtained almost immediately, and the determination can be performed by doctors or nurses trained to use the device.[3]

The functioning of transcutaneous bilirubinometers is based on directing white light toward the skin of the newborn and measuring the intensity of the specific wavelengths returned. Knowing the spectral properties of the components of skin, they are subtracted from the components that cause interference and the concentration of bilirubins is determined. In recent years improvements in transcutaneous bilirubinometers have helped increase the precision of their results.[4-6]

Traditionally, it has been preferred to choose a single anatomical region to measure total transcutaneous bilirubin (TTB) in newborns, usually the forehead;[7,8] when measurements are taken at more than one site the results that show the lowest correlation with total serum bilirubin (TSB) have been discarded losing data.[9-13] Modern bilirubinometers are more ergonomic and measurements can be taken in different anatomical areas. Using more than one site for measurements on the same individual provides us with several determinations of TTB which can be used simultaneously in a predictive model of TSB.

The objective of this study was to prove the usefulness of a predictive model of TSB which includes simultaneous measurements of TTB on forehead and chest, in premature and term neonates.

MATERIAL AND METHODS

A transverse and analytical study conducted at the rooming in, pathological nursery, and neonatal intensive care of Hospital de la Mujer del Instituto de Servicios de Salud del Estado de Aguascalientes, from January 21 through April 30, 2013. This hospital attends an average of 10 800 births a year, 10% of them premature.

Newborns eligible for inclusion in the study had gestational age between 30 and 42 weeks (cataloged by the Capurro A method), birth weight of 1 000 g or more, and quantification of serum bilirubins.

Those that received phototherapy or any blood product before the TSB or TTB measurement were excluded. Patients with samples deemed inadequate or with more than two hours before processing, with suspicion or diagnosis of any kind of dysmorphic syndrome, congenital heart disease, or transfer to another hospital were eliminated. The clinical file was used to obtain demographic data in each case and an individual data collection sheet was used.

For TSB determinations the attending physician or a nurse obtained from each patient 500 microliters of blood by puncture of a peripheral vein. The blood was collected in a dry tube covered on the outside with carbon paper to protect the sample from contact with light. Samples for TSB were processed in the hospital's clinical laboratory by photometric method (Cobas Integra System 400plus, Roche Diagnostic). All determinations of TTB on forehead and chest were made with a single Bilichek device (Philips Children´s Medi-

cal Ventures) by medical personnel trained in its use and in accordance with the manufacturer's instructions. Measurements were taken no more than 30 minutes before or after taking the blood sample. Results for TSB and TTB were reported in mg/dL.

Results were analyzed with the statistical software R. The independent variables in the analysis were: total transcutaneous bilirubins forehead (TTBf), total transcutaneous bilirubins chest (TTBs), gestational age (AGEg), birth weight (WEIGHT), and hours of life (HOURSl) at the time of bilirubin determinations. The dependent variable was total serum bilirubins (TSB). Pearson correlations between TSB/TTBf and TSB/TTBs were determined and linear regression analyses were conducted for one or several independent variables.

The neonates received care under usual hospital management protocols. Informed consent was obtained from at least one of the parents. The study was reviewed and approved by the State Research Committee, which corroborated compliance with the bioethical criteria of safety and risk for research in humans in accordance with the General Law on Healthcare. All the information obtained was strictly confidential. The authors of this manuscript had no conflicts of interest of any kind.

RESULTS

One hundred and eleven simultaneous determinations of TSB/TTB on forehead and chest were made in 105 patients. Twenty-two simultaneous determinations were eliminated: 10 due to late processing of serum bilirubins, 6 due to misplaced files, 2 due to misplaced data collection sheets, 1 due to use of blood products in the patient, and 3 due to diagnosis of trisomy 21. The summarized statistics from the data collected in the study for the 89 remaining samples are shown in Table 1.

Table 1. Statistical summary of 89 observations in the study

Variable	Mean	Standard deviation	Minimum value	Maximum value
TSB (mg/dL)	9.0	2.8	3.5	16.0
WEIGHT (g)	2540.4	672.5	1000.0	4400.0
AGEg (weeks)	36.2	2.4	32.0	41.1
HOURSl (hours)	48.6	30.8	9.0	275.0
TTBf (mg/dL)	9.8	3.4	2.7	19.6
TTBs (mg/dL)	11.0	3.5	3.1	19.9

TSB: total serum bilirubins; WEIGHT: birth weight; AGEg: gestational age; HOURSl: hours of life at time of bilirubin determinations; TTBf: total transcutaneous bilirubins with measurement taken on the forehead; TTBs: total transcutaneous bilirubins with measurement taken on the chest.

The correlation of TSB and TTBf samples was 0.8411 and for TSB and TTBs samples was 0.7942, both statistically significant correlations ($p < 2.2$ E-16 in both cases). The existence of a significant correlation led us to propose a linear model to predict the value of TSB based on TTB.

A simple regression analysis was conducted between TSB and TTBf, obtaining the linear model that we call "simple model with TTBf," TSB $= 2.1187 + 0.7035 \times$ TTBf. The same analysis was repeated taking TTBs as independent variable, obtaining the linear model that we call "simple model with TTBs," TSB $= 2.0405 + 0.6349 \times$ TTBs; both models were statistically significant with associated F values of 210.4 and 148.6, respectively, and $p < 2.2$ E-16 in both cases. The first two lines of Table 2 show the values of standard error, R^2 and $R^2_{adjusted}$ for these models.

To simultaneously take into account the TTB measurements, a multiple linear regression analysis was conducted of TSB *vs*. TTBf and TTBs including, in addition, the rest of the variables in the study (WEIGHT, AGEg, HOURSl). The linear model obtained, which we call "complete model," was TSB $= -2.630 - 4.298$E-05 $\times$ WEIGHT $+ 0.115 \times$ AGEg $+ 6.861$E-04 $\times$ HOURSl $+$

$0.472 \times$ TTBf $+ 0.265 \times$ TTBs. This model had an associated F value of 46.33 and was statistically significant ($p < 2.2$ E-16). The values that complement the analysis are shown in the third line of Table 2.

In order to eliminate from the model those variables that do not provide significant data, the method of eliminating variables backward was used.[14] Using this method the variables WEIGHT (p value 0.9139), HOURSl (p value 0.9023), and AGEg (p value 0.1267) were removed from the model, sequentially. The linear model obtained, which we call "reduced model," was TSB = 1.620 + 0.503 ´TTBf + 0.224 ´TTBs. This model had an associated F value of 115.5 and was statistically significant ($p < 2.2$ E-16) and, as we can see, only included TTB measurements to predict the value of TSB. It is relevant that the last variable eliminated from the model was AGEg, with a p value of 0.1267, much less than the p value of the other variables eliminated from the model. The values that complement the analysis in this model are shown in the fourth line of Table 2.

ANALYSIS

Predictive linear models of TSB were obtained which used simultaneous measurement of transcutaneous bilirubins on forehead and chest. Because the values of the coefficients of determination R^2 and $R^2_{adjusted}$ for the complete and reduced models were greater than those corresponding to the simple models with TTBf and TTBs (Table 2), a model that simultaneously includes the two TTB measurements allows us to obtain a better prediction of TSB than with models that include only one of the measurements. Although the complete model had a better value of R^2 than the reduced model, the values of $R^2_{adjusted}$ and the standard error are better in the latter model. Also, because it has fewer independent variables, the reduced model is less susceptible to errors in data collection.

Few studies have been published on the TSB/TTB correlation in Hispanic populations; [3,13,15] ours confirmed that the correlation is present in our population and is higher in measurements taken on forehead than on chest, as reported in the study conducted by Jimenez-Pena et al.[3] The correlations obtained were smaller than those found in that study due to the different models of bilirubinometer used and the greater diversity of individuals studied (see Table 1) on including neonates under 35 weeks of gestational age and with lower weights.

Because our study has a predictive, more than an explicative, focus, we sought to obtain, from among a set of variables, those most effective in predicting TSB results, for which purpose the reduced model dispensed with variables associated with patients' gestational age, weight, and hours of life, because their contribution was not significant for the pre-

Table 2. Results of linear regression for the different models in the study

Model	Standard error	R^2 (%)	$R^2_{adjusted}$ (%)	F	p Value
Simple with TTBf	1.537	70.75	70.41	210.4	< 2.2E-16
Simple with TTBs	1.727	63.07	62.65	148.6	< 2.2E-16
Complete	1.494	73.62	72.03	46.33	< 2.2E-16
Reduced	1.488	72.87	72.24	115.5	< 2.2E-16

R^2: coefficient of determination of the model; $R^2_{adjusted}$: coefficient of determination of the model adjusted to sample size and number of independent variables; F: value of statistic from test of significance of the model; p Value: value of significance associated with the test using the statistic F. All the models are linear with dependent variable TSB. The complete model includes all the independent variables in the study and the reduced model only the variables BBTf and TTBs.

diction sought. One of the variables eliminated was gestational age, which is taken into account in hyperbilirubinemia management protocols. It is noteworthy that the variable associated with gestational age was the last to be eliminated to obtain the reduced model, being barely insignificant, based on which we suspect that with more data from premature and term neonates the variable offers a significant contribution to the model when combined with TTB on forehead and chest.

Given that in the models obtained the values for standard error are relatively high (greater than one unit) and those for coefficients of determination low (less than 80%), it is considered necessary to replicate the analysis with a larger sample which includes both premature and term infants, to construct a predictive model that allows us to make inferences in our population with a smaller margin of error.

As an additional result of the study it was proven that, even in smaller and less stable patients, determinations in the chest can be made taking only a few seconds longer in the process.

Due to the manner in which the sample was formed, the applicability of the results of this study is limited to conditions of diet and exposure to natural and artificial light of neonates who remained hospitalized during the determinations of bilirubins.

In conclusion, this study showed the usefulness of simultaneous measurement of TTB on forehead and chest in constructing a predictive model of TSB, in contrast to the international literature, which has opted to consider only measurement at one anatomical site. In clinical practice the model to implement would be:

1. Obtaining TTBf and TTBs measurements using a bilirubinometer on the neonate's forehead and chest.

2. Estimating TSB by substituting the TTBf and TTBs values obtained in the formula from the reduced model (TSB = $1.620 + 0.503 \times$ TTBf $+ 0.224 \times$ TTBs).

3. Using the estimated TSB, obtained by means of the predictive model, in continuing the protocol for management of hyperbilirubinemia in newborns.

To show the practical application of these three steps we take as example a neonate with 48 hours of life, birth weight 2,750 g, and gestational age 36 weeks. TTBf and TTBs measurements of 7.1 mg/dL and 9.5 mg/dL, respectively, were obtained with the bilirubinometer. Serum bilirubins were estimated using the formula from the reduced model:

$$TSB = 1.620 + 0.503 \times TTBf + 0.224 \times TTBs$$

$$TSB = 1.620 + 0.503 \times 7.1 + 0.224 \times 9.5$$

$$TSB = 7.3193$$

With this estimate of TSB, and following the protocol for management of hyperbilirubinemia in newborns, this patient was not a candidate for collection of a blood sample to corroborate total serum bilirubins or considered eligible for phototherapy.

We also concluded that further studies are needed to generate various predictive models that have a smaller margin of error and are better suited to each particular group of neonates. When such predictive models can be validated, they can be used to decide in which patients it is necessary to make TSB determinations at this time and in which it they are not needed, all as part of strategies for prevention of bilirubin-induced neurotoxicity in newborns.

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