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A DOSE-RESPONSE MODEL FOR THE CONVENTIONAL PHOTOTHERAPY OF THE NEWBORN

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ABSTRACT. Jaundice of the newborn is a common problem as a consequence of the rapid increment of blood bilirubin in the first days of live. In most cases, it is considered a physiological transient situation, but unmanaged hyperbilirubinemia can lead to death or serious injuries for the survivors. For decades, phototherapy has been used as the main method for prevention and treatment of hyperbilirubinaemia of the newborn. This work aims at finding a predictive model for the decrement of blood bilirubin for patients submitted to conventional phototherapy. Data from the phototherapy of 90 term newborns were collected and used in a multiple regression method. A rigorous statistical analysis was done in order to guarantee a correct and valid model. The obtained model was able to explain 78% of the variation of the dependent variable. We show that it is possible to predict the total serum bilirubin of the patient under conventional phototherapy by knowing its birth weight, bilirubin level at the beginning of treatment and the radiant energy density (dose). Besides, it is possible to infer the time necessary for a given decrement of bilirubin, under approximately constant irradiance. Statistical analysis of the obtained model shows that it is valid for several ranges of birth weight, initial bilirubin level, and radiant energy density. It is expected that the proposed model can be useful in the clinical management of hyperbilirubinemia of the newborn.

KEY WORDS. dose-response, spectral irradiance, hyperbilirubinemia, phototherapy, monitoring.

INTRODUCTION

Jaundice is the commonest clinical condition of the newborn during the first week of life. It is observed in 80% of the preterm and 60% of the term newborns (corresponding to those born before and after the 37th gestation week, respectively). This condition, named hyperbilirubinemia, is mainly resulting from a high level of total serum bilirubin (TSB), related to the non-conjugated fraction. In most cases, jaundice is a physiological condition that disappears by itself after some days without affecting the newborn's health. However, it is estimated that around 3 to 6% of these cases require clinical care [1, 2]. Hyperbilirubinemia can lead patient to a serious encephalopathy known as kernicterus [3]. It has a high morbity and survivors of this pathology can present serious problems, like coreoathetosis, deafness, and mental impairment [4, 5]. Despite of the advancement of medicine, kernicterus, as consequence of unmanaged hyperbilirubinemia of the newborn, is still an issue of current concern [3, 6].

A half century ago, since the efficacy of phototherapy was proved, it has become the main method for the prevention and treatment of the newborn's hyperbilirubinemia

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[2, 7]. Much progress has been done in this area, especially towards the study of spectral irradiance with different type and number of lamps in the phototherapy equipments [2, 8]. Around three decades ago, it was suggested that, once the radiant energy density (or simply, the accumulated dose) can be measured, it could be possible to predict the average decreasing of blood concentration of bilirubin in the first 24 hours of conventional phototherapy [9, 10]. However, not much research about this subject has been done, in the quest for a predictive model relating the decrement of bilirubin to phototherapy parameters or, in short, a dose-response model. Therefore, the objective of this work is to find a predictive model of the decrement of bilirubin in the newborn, as response to a given exposition to the conventional phototherapy.

PATIENTS AND METHODS

Sampling

During May to September/2003, a total of 107 newborns were submitted to a controlled conventional phototherapy at the Hospital Universitário do Oeste do Paraná, in Cascavel, Brazil, a reference regional hospital. A proper informed consent obtained from parents of patients was a qualifying criterion to be included in this research (see next section). Later, 17 newborns were excluded of the study due to the following: two required to be changed to double phototherapy since their bilirubin levels were too high; the other 15 were excluded due to the detection of spectral irradiance under the minimum limit stated in the research protocol. For the remaining 90 newborns effectively included in the study, the average birth weight (BW) of the group was 2650 ± 0.74 g. Table 1 shows how the group was divided into categories according to birth weight.

Regarding the indication of the phototherapy, for 4 (4.44%) patients it was indicated prophylactically, and for 86 (95.56%) it was indicated therapeutically. In this last group, 12 (13.95%) had early indication, and 74 (86.05%) started phototherapy lately.

Research protocol and eligibility criteria

Prior starting to collect data, eligibility, non-eligibility and exclusion criteria were defined and stated in the research protocol to be followed. Eligibility criteria qualify prospective patients to be included in the research. Non-eligibility criteria do not qualify. Exclusion criteria eliminate those subjects previously qualified and included, after the research has begun. Patients were eligible to be included in the research if they satisfied the following criteria:

(a) All newborn with BW $\geq$ 1200 g;
(b) Hemolytic disease since the beginning of indirect hyperbilirubinemia;
(c) BW $\leq$ 1500 g, regardless of TSB concentration, starting at around 24 hr of life (prophylactic phototherapy);
(d) 1501 g $\leq$ BW $\leq$ 2000 g, with indirect hyperbilirubinemia (early indication);
(e) 2001 g $\leq$ BW $\leq$ 2500 g, if TSB $\geq$ 10 mg/dL (late indication);
(f) 2501 g $<$ BW, if TSB $\geq$ 15 mg/dL (or less than this, if it is supposed that TSB will reach this value within the next 24 hr) [11].

For any case mentioned before, newborns having haemolysis or aggravating factors prone to increased risk of kernicterus, the TSB threshold was decreased 2 mg/dL to be indicated to phototherapy. Aggravating factors were: 5 min Apgar index below 3, hypoglycaemia, hypothermia, hypercapnia, hypoxaemia and/or persistent acidosis, sepsis and/or meningitis [11, 12].

For this research, the non-eligibility criteria were:

(a) BW $<$ 1200 g;
(b) Current use of phenobarbitone either by mother or child [13];
(c) Initial indication of double or triple phototherapy;
(d) Newborn submitted to blood transfusion;
(e) Newborn with congenital defect; hereditary disease of erythrocytes or autoimmune disease with intense haemolysis.

Eligible patients could have been excluded from the research due to the following exclusion criteria:

(a) Registering spectral irradiance below 4.0 μW/cm^2/nm in any of the measurements [12, 14, 15];
(b) Changing modality of phototherapy to double or triple;
(c) Technical or clinical impossibility to determine TSB;
(d) Death during the period of phototherapy.

MEASUREMENTS

All patients were submitted to phototherapy continuously, except during bath, breast-feeding, blood sampling for laboratory tests, endotracheal intubation and thoracic draining. All newborns were kept in single or double-wall incubators without lateral cover, without diapers and with proper opaque ocular protection [16, 17].

Table 1. Patients included in the study classified according to the birth weight

Group	Acronym	Definition	Number of subjects	Percent of total
Very low	VLBW	BW < 1500 g	5	5.56%
Low	LBW	$1500\,\text{g} \leq \text{BW} \leq 2499\,\text{g}$	31	34.44%
Normal	NBW	$2500\,\text{g} \leq \text{BW}$	54	60%

Direct and indirect bilirubin (respectively, DB and IB) were measured at the moment the patient started phototherapy (this time is named T_1), when TSB was first determined (TSB_1), and also in two further blood samples (at times T_2 and T_3). The second blood sample (TSB_2) was always collected in the following morning (T_2), at least 12 hr far from T_1. In the same way, the third blood sample (TSB_3) was collected in the next morning (T_3), around 24 hr far from T_2.

Both bilirurin were measured using Sims-Horn methodology, using a 50 μL sample. In this methodology, the maximum absorbance is in 525 nm, thanks to the red azobilirubin formed. According to the supplier (Labtest Diagnóstica, Rio de Janeiro), the specificity of the test is 3.9%, compared with a similar method. Also, using the absorbance of the pattern as parameter, the photometric detection limit is 0.02 mg/dL for both DB and IB, corresponding to 0.001 of absorbance.

For each subject, the last data collected was at the 3rd blood sample (T_3), regardless the continuity or not of the treatment. Usually, this time occurred around 36 hours after the beginning of phototherapy. In some cases phototherapy was stopped before T_3, when the clinician considered the decrease of bilirubin in the first 24 hr as a reliable parameter to discharge patient from phototherapy [10].

The phototherapy unities used (FANEM Ltda, São Paulo) had the same number and type of fluorescent lamps: 2 daylight (Fanza T10, 20 watts) in the sides, and 4 blue (Sylvania F20W T12/AZ, 20 watts) in the center. Lamps were centered and arranged transversally according to the axis of the incubator. The distance between lamps and the bed surface was kept in 36 cm.

Due to the irregular distribution of irradiance on the plane where the patient is laid down, an average measurement was done [18, 19], as follows. The projection of the light in the bed was divided into 9 rectangles of same area, and the spectral irradiance was measured in the center of each rectangle. The final value considered was the average over all 9 measurements. All additive influence in the measurements was properly avoided, by closing curtains, turning off environmental lighting and other surrounding phototherapy unities [20].

A calibrated radiometer Model 620 (FANEM Ltda, São Paulo) was used for all spectral irradiance measurements in $\mu\text{W/cm}^2\text{/nm}$. This radiometer has a narrow spectral response curve between 380 and 530 nm (10% points), with peak in 450 nm.

The mean spectral irradiance reported in each period (T_1 to T_2 and T_2 to T_3) was obtained by averaging all measurements during the period considered. The total exposition time (T_T) of the newborn to phototherapy was obtained by adding the time between blood samplings and decrementing the time the newborn was not submitted to phototherapy (as mentioned before). By convention, the time between T_1 and T_2 is called first period and between T_2 and T_3, the second period.

Computation of the radiant energy density

Although radiant energy (given in Joules) is not a derived SI (International System of Units) unit, it is of crucial importance for this study [21]. Radiant energy is defined as the product of radiant flux by the exposition time and, frequently, and it is understood as the total dose received by the patient.

In this work, the radiant energy density (RED) effectively delivered to the newborn during phototherapy was obtained by computation, according to the following procedure [15, 22]. The radiometer used in this work effectively measures spectral irradiance that is converted to irradiance, taking into account the spectral response curve of the optical device (including optical filters and optical sensor). To obtain radiant energy density, irradiance is integrated along time. Considering that irradiance measurements in the clinical setting are done at n sparse moments, not necessarily equidistant, that is, $E(t_0)$, $E(t_1)$,..., $E(t_{n-1})$. The easiest way to compute the discrete integral of irradiance is taking the average value between two successive measurements and multiplying by the time elapsed between them (say, t_i and t_{i-1}), and then summing up all these products along all $n-1$ measurements. Therefore, RED can be computed by Equation (1):

$$Q_d = \sum_{i=1}^{n-1} \left[\frac{E(t_i) + E(t_{i-1})}{2} \right] \cdot [t_i - t_{i-1}] \tag{1}$$

Statistical procedure

The predictive model was obtained using a multiple regression technique, considering as dependent variable the value of total bilirubin at the time of the last observation (TSB_T, in mg/dL). The following independent variables were investigated: birth weight (BW), gestational age (GA), age at the moment of admission in the protocol (Age), total exposition time to phototherapy (T_T), TSB at the moment of admission in the protocol (TSB_1), and radiant energy density (RED). Models obtained using these independent variables altogether did not achieved statistical significance using tests *F* and *t*. This fact led to the creation of a new variable, resulting from the interaction between RED and BW. This new variable was named REDBW and was defined as the product of RED by BW (given in $g \cdot J/cm^2$).

The set of independent variables studied was submitted to the backward elimination technique [24] that pointed out only three variables with statistical significance: BW, TSB_1 and REDBW. Hence, the other independent variables (GA, Age, T_T and RED) were excluded from the multiple regression model.

The evaluation of the regression model adjusted to data and the potential violations of the underlying assumptions of the model (normal distribution, homocedasticity, error independence and linearity) were done by residues analysis [25]. Autocorrelation of residues was investigated with the Durbin-Watson statistics, and a diagram of standardized residues as function of the time that observations occurred.

The corrected multiple determination coefficient (R^2 corrected) was used to compute the percent of variation of the independent variable that is explained by the regression model. Finally, multicolinearity was investigated by computing the variance inflation factor (VIF), for each of the independent variables used in the predictive model.

RESULTS

Most values presented in this section represent the mean value followed by the symbol "±" and the corresponding standard deviation.

In the first period, 90 newborns were submitted to phototherapy during 20.53 ± 4.45 hr, whereas in the second period, there were 78 newborns, during 19.34 ± 8.06 hr. The average spectral irradiance (for all measurements of all patients) in each period was, respectively, 4.61 ± 0.31 and 4.54 ± 0.32 $\mu W/cm^2/nm$. Similarly, the average DER was 28.70 ± 6.66 and 26.59 ± 11.19 J/cm^2. As consequence of phototherapy, the average decrement of TSB was 2.05 ± 1.88 mg/dL in the first period, and 1.54 ± 1.54 mg/dL in the second one. These values correspond, respectively, to 16.12 ± 7.55% and 12.82 ± 6.17%. At the end of the observation period, the average TSB was 9.68 ± 2.21 mg/dL, indicating a decrement of 25.42 ± 9.22%, related to the initial value, at the beginning of phototherapy. Comparing the two periods, in the first one the decrement of TSB was larger than in the second, as expected, but the decrement difference was not statistically significant (test $t = -0.95070018 < t_{178} = 2.603738$, at significance level 0.01).

Regression analysis presented the following results: R^2 corrected: 0.78 and standard error: 1.03. The analysis of the standard residues for each of the selected independent variables did not show any clear pattern (such as concentration in a given region of the plot of residues), thus suggesting homocedasticity. A plot of residues versus estimated values showed points randomly distributed, without any clear pattern, and values close to zero. This suggests that the underlying assumptions of the regression model were satisfied [24]. In the same way, the observation of residues according to the order data were collected did not presented any clear pattern indicating autocorrelation. The Durbin-Watson statistics, whose value was 1.810, support the assertion that there is no correlation among residues.

Variance analysis (ANOVA), for the significance level 0.01, resulted in $F = 105.765 > F_{s(3,86)} = 2.68$ and *p*-value smaller than 0.01. These results demonstrate that there is a significant relationship between the dependent variable and the set of independent variables.

Table 2 shows the results of the test of hypothesis for the coefficients for the three independent variables. For the three variables, *t*-test is larger than the critical value for *t*, +1.6628 and −1.6628 for 86 degrees of freedom and significance level of 0.01. Hence, for all independent variables (BW, TSB_1 and REDBW) the null hypothesis (H_0: $\beta_i = 0$) is rejected. The coefficients of the predictive model are drawn from this table, and presented in Equation (2).

$$TSB_T = 1.110232 + 0.0007717 \cdot BW + 0.560913 \cdot TSB_1 - 0.000006 \cdot REDBW \quad (2)$$

This equation gives the relationship between the total bilirubin at a given time under phototherapy (TSB_T, in mg/dL) as function of TSB at the beginning of treatment (TSB_1, in mg/dL), birth weight (BW, in g) and the product of the radiant energy density by the birth weight (REDBW, in $g \cdot J/cm^2$). The exposition time is implicit in the computation of REDBW by Equation (1).

The study of the variance inflation factor (VIF) for each variable of the final model showed values lower than 5, thus eliminating the possibility of multicolinearity in data.

A test of hypothesis for verifying the statistical significance of the difference between two means (μ_1 e

Table 2. Test of hypothesis for the coefficients of the independent variables in the regression model

	Coefficients	Standard error	test *t*	*p*-value
Intersection	1110.2E-03	516.0E-03	2.152	34.2E-03
BW	771.7E-06	222.0E-06	3.475	803.0E-06
TSB_1	560.9E-03	40.1E-03	13.999	6.8E-24
REDBW	−6.0E-06	3.3E-06	−1.812	73.4E-03

μ_2) was used to verify the null hypothesis (H_0: $\mu_1 = \mu_{2)}$, for the significance level of 0.01. This test did not rejected the null hypothesis for the following conditions: BW $<$ 2000 g and BW $\geq$ 2000 g; BW $<$ 2500 g and BW $\geq$ 2500 g; REDBW $<$ 100000 g.J/cm^2 and REDBW $\geq$ 100000 g.J/cm^2. For these three conditions, test *t* was, respectively: $t = -0.35577 < t_{88} = 2.63286$; $t = -0.433067916 < t_{88} = 2.632859832$; and $t = 0.730130378 < t_{88} = 2.632859832$. In the same way, a test of hypothesis and ANOVA (with significance level 0.01) for multiple groups (BW $<$ 2000 g; 2001 g $\leq$ BW $\leq$ 3000 g; BW $>$ 3001 g) did not reject the null hypothesis, since test $F = 0.593308 < F_{\text{tab}(2.87)} = 4.857782$.

DISCUSSION AND CONCLUSIONS

Results obtained in this work could be compared with other works only if the same methodological procedures were adopted. In special, the adoption of different initial TSB level for starting phototherapy and irradiance levels can be important factors to be taken into account for other similar works. Anyhow, our results are in accordance with current literature and clinical knowledge regarding the pronounced decrement of TSB in the first 24 hr of treatment under conventional phototherapy.

The minimum acceptable value for irradiance during phototherapy established in the protocol (4 μW/cm^2/nm) was achieved for 90 newborns (84.12%) out of the 107 ones initially included in the study. All fluorescent lamps were changed approximately after 100 hours of use, according to what is currently recommended [23]. We observed that lamps deteriorate faster than expected under normal conditions, possibly due to its low quality [26]. This fact strongly suggests the need for a continuous monitoring of irradiance in the phototherapy of the newborn, so as to enable phototherapy to achieve its efficacy for the treatment.

ANOVA analysis demonstrated that the obtained model using independent variables BW, TSB_1 and REDBW has statistical significance ($p < 0.01$) and also, the test *t* showed that all variables are significant. Analysis of residues indicates that the main underlying assumptions of the regression model were satisfied.

Results of test *t* for different BW groups, different TSB_1 groups and different REDBW groups showed no significant differences. This fact assures that the obtained model is valid for any of the ranges tested.

Multiple regression analysis was adequate for obtaining a valid model using the collected data. The obtained predictive model (Equation (2)) does explain the dependent variable (TSB_T) in 78%. Hypothesis tests, at significance level 0.01, showed that there are no differences in TSB_T estimates for all studied ranges of BW, TSB_1 and REDBW, suggesting the generality of the obtained model. Therefore, the proposed prediction model met the main objectives of this research. It is possible to predict TSB, by knowing newborn's BW, TSB at the beginning of phototherapy, the duration of exposition to phototherapy, and the average irradiance. This is the essence of a dose-response relationship. Besides, it is possible to estimate the time necessary for a given decrement of TSB, under approximately constant irradiance.

It is expected that the proposed predictive dose-response model can contribute to improve the clinical management of hyperbilirubinemia. Particularly important is the potential reduction of the number of blood samples necessary to the clinical control of hyperbilirubinemia, minimizing discomfort and risks to the newborn.

Future work will include a multicenter prospective study, aiming at confirming the validity and usefulness of the proposed dose – response predictive model for the phototherapy of the newborn.

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