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Phototherapy of the Newborn: a Predictive Model for the Outcome

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Abstract— **Jaundice in one of the most common problems of the newborn. In most cases, jaundice is considered a physiological transient situation, but sometimes it 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 followed conventional phototherapy. Data from 90 patients were collected and used in the 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 found that it is possible to predict the total sugar bilirubin of the patient under phototherapy by knowing its birth weight, bilirubin level at the beginning of treatment, duration of exposition, and irradiance. Besides, it is possible to infer the time necessary for a given decrement of bilirubin, under approximately constant irradiance.**

I. Introduction

JAUNDICE is the commonest clinical condition in 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) This condition is mainly resulting from a high level of total serum bilirubin – TSB (hyperbilirubinaemia), related to the non-conjugated fraction. [2], [5]. 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, due to the high risk of kernicterus, an encephalopathy with high morbidity. Survivors of this pathology can present serious problems, like coreoathetosis, deafness, and mental impairment [11]. A half century ago, since the efficacy of phototherapy was proved, it has become the main method for prevention and treatment of the hyperbilirubinaemia of the newborn [5]. 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]. Three decades ago, Mims et al [9] suggested that, once the radiant energy density (or simply, the accumulated dose) can be measured, it could be possible to preview the average decreasing of blood concentration of bilirubin in the first 24 hours of phototherapy. However, very few research about this subject has been done since then, in the quest for a predictive model relating the decrement of bilirubin to phototherapy parameters [10]. Therefore, this work aims at finding a predictive model for the decrement of the serum bilirubin as response to the conventional phototherapy of the newborn.

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II. Methodology

A. Sampling

A total of 90 newborns were submitted to conventional phototherapy at the Hospital Universitário do Oeste do Paraná, in Cascavel, Brazil, during may-september/2004. A proper informed consent obtained from parents was a qualifying criterion to be included in this research. The average birth weight (BW) of the group was 2650 ± 0.74 g. Divided into weight ranges, this was the profile of the group: 5 (5.56%) very low birth weight – VLBW (BW < 1500 g), 31 (34.44%) low birth weight – LBW (1501 g ≤ BW ≤ 2499 g), and 54 (60%) normal weighted infants – NBW (BW ≥ 2500 g). Regarding the indication of phototherapy, for 4 (4.44%) patients it was prophylactic and for the remaining 86 (95.56%) it was therapeutic.

B. Protocol and eligibility criteria

Patients were eligible to be included in the research if they satisfied the following criteria: (a) BW ≥ 1200 g for any case; (b) hemolytic disease since the beginning of indirect hyperbilirubinaemia; (c) BW ≤ 1500 g, regardless of TSB concentration, starting at around 24 h of life (prophylactic phototherapy); (d) 1501 g ≤ BW ≤ 2000 g, with indirect hyperbilirubinaemia (early indication); (e) 2001 g ≤ BW ≤ 2500 g, if TSB ≥ 10 mg/dL (late indication); (f) 2501 g < BW, if TSB ≥ 15 mg/dL (or less than this, if it is supposed that it will reach this value within the next 24 hours) [2].

The non-eligibility criteria were: BW < 1200 g; current use of phenobarbitone by either mother or child; indication of double or triple phototherapy; newborn submitted to blood transfusion; newborn with congenital defect; hereditary disease of erythrocytes or autoimmune disease with intense haemolysis. Eligible patients could have been excluded during the research due to the following exclusion criteria: registering spectral irradiance below 4.0

$\mu W/cm^2/nm$ [1], [5], [7]; changing modality of phototherapy to double or triple; impossibility to determine TSB and death during phototherapy and death during phototherapy.

For each subject, data were collected until the 3rd blood sample (T_3), regardless the continuity of treatment. Usually this time was around 36 hours after the phototherapy has begun. In some cases phototherapy has been stopped before T_3, considering that the decrease of bilirubinemia in the first 24 hours is a reliable parameter to discharge patient from phototherapy [10]. All patients were under phototherapy continuously, except during bath, breast-feeding, blood sampling, intubations or other clinical procedure. Newborns were kept in single or double-wall incubators without lateral cover, without diapers and with opaque ocular protection [3], [8].

The phototherapy equipment 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 the axis of the incubator. The distance between lamps and the bed surface was kept fixed in 36 centimeters.

Direct and indirect bilirubins were measured at the moment the patient was included in the research (T_1), when TSB was first determined (TSB_1). Also, two other blood samples were done (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 hours far from T_1. In the same way, the third blood sample (TSB_3) was collected in the next morning (T_3), around 24 hours far from T_2.

Both bilirubin was measured using Sims-Horn methodology, using a 50 µL of blood sample. In this methodology the maximum absorbance is in 525 nm, thanks to the red azobilirubin formed.

The total exposition time (T_t) of the newborn to phototherapy was obtained by summing the time between blood sampling. By convention, the time between T_1 and T_2 is called first period and between T_2 and T_3, the second period. All time the newborn was not submitted to phototherapy (as mentioned before) was subtracted in the computation of T_t. The mean spectral irradiance in each period (T_1 to T_2 and T_2 to T_3) was obtained by averaging all measurements during the period considered. All additive influence in the measurements was properly avoided, by closing curtains, turning off environmental lighting and other surrounding phototherapy equipments. A calibrated radiometer, Model 620 (FANEM Ltda, São Paulo), was used for all spectral irradiance measurements in $\mu W/cm^2/nm$. This radiometer has a narrow spectral response curve between 380 and 530 nm (10% points), with peak in 450 nm.

C. Computation of the radiant energy density

The radiant energy density (RED), given in J/m^2, effectively delivered to the newborn during phototherapy was obtained by computation. The first step is transforming the measured spectral irradiance (E_e) into irradiance (E), considering the wavelength range (λ) and the spectral response curve of the optical device (including optical filters and optical sensor), supplied by the radiometer's manufacturer.

Considering that irradiance may not be constant between intervals T_1-T_2 and T_2-T_3, and it is, in fact, sampled many times within intervals, RED can be obtained with equation 1, for the n measurements done at discrete time (t_i), where R is a conversion constant for scale adjustment described in [7].

$$DER = R.\sum_{i=1}^{n-1}\left[\frac{E(t_i)+E(t_{i-1})}{2}\right].\left[t_i - t_{i-1}\right] \quad (1)$$

D. The predictive model

The predictive model was obtained by means of the multiple regression technique, considering as dependent variable the value of TSB, in mg/dL, by the time of last observation (TSB_t). Several independent variables were studied: birth weight (BW), in grams; gestational age (GA), in weeks; age at the moment of admission in the protocol (Age), in hours; total exposition time to phototherapy (Tt), in hours; TSB at the moment of admission in the protocol (TSB_1), in mg/dL; and radiant energy density (RED), in J/cm^2. Models obtained using these independent variables altogether did not achieved significance using test F and test t. This fact led to the inclusion of a new variable, resulting from the interaction between RED and BW. This new variable was named REDBW and was defined simply as the product of RED by BW, in $g.J/cm^2$.

The set of independent variables studied was submitted to a technique named backward elimination, which pointed out only three variables with statistical significance: BW, TSB_1, REDBW. Since the other independent variables (GA, Age, T_t and RED) were not significant, they 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 using residues analysis. Autocorrelation of residues was investigated using a standardized residues diagram as function of the time of observations, and also, the Durbin-Watson statistics [4].

III. Results and Statistical Analysis

In the first period, 90 newborns were submitted to phototherapy during 20.53 ± 4.45 hours, and, in the second period, there were 78 newborns, during 19.34 ± 8.06 hours. The average spectral irradiance 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, TSB decreased, in average 2.05 ± 1.88 mg/dL in the first period, and 1.54 ± 0.74 mg/dL in the second. 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%, relative to the initial value at the beginning of phototherapy. Comparing both periods, in the first one the decrement of TSB was larger than that in the second, but the difference was not statistically significant using test-*t*, with significance level 0.01.

Regression analysis presented the following results: R^2: 0.79; corrected R^2: 0.78; standard error: 1.03.

The diagram of expected values versus residues showed points distributed along the straight line (45º), representing the normal distribution. The analysis of the standard residues for each of the selected independent variables also did not shown any clear pattern (such as concentration in a given region of the plot), thus suggesting homocedasticity. The observation of residues plot for the estimated values confirms that the underlying assumptions of the regression model were met. The set of points were randomly dispersed, and closer to zero, revealing normal distribution. The Durbin-Watson statistics, whose value was 1.810, support the assertion that there is no correlation among residues.

Analysis of variance (ANOVA), for significance level of 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.

The test of hypothesis for the coefficients for the three independent variables is shown in table 1. For all variables, *t*–test is larger than the critical value for *t*, with significance level of 0.01. Hence, for all the three independent variables (BW, TSB_1 and REDBW) the null hypothesis (H_0: $\beta_i = 0$) is rejected.

Table 1: Test of hypothesis for the coefficients of independent variables.

Variable	Value	Standard error	t	p-value
k	1110.2E-03	516.0E-03	2.152	34.2E-03
a	771.7E-06	222.0E-06	3.475	803.0E-06
b	560.9E-03	40.1E-03	13.999	6.8E-24
c	-6.0E-06	3.3E-06	-1.812	73.4E-03

The coefficients of the predictive model for the decrement of bilirubin are drawn from table 1. The model is presented in equation 1, where TSB_t and TSB_1 are in mg/dL, BW is in grams and REDBW is in g.J/cm^2. In this equation, *k* is the intersection point and *a*, *b* and *c* are the coefficients of the independent variables.

$$TSB_t = k + a.BW + b.TSB_1 + c.REDBW \quad (2)$$

This equation establishes the relationship between the TSB at a given time under phototherapy as function of the TSB at the beginning of treatment (TSB_1), birth weight (BW) and the product of the accumulated radiant energy density by the birth weight (REDBW). The time at which TSB is predicted is implicit in RED, since its computation is a function of the exposition time and the irradiance.

The prediction efficiency index, using the coefficient of multiple determination was ≅ 77.

A test of hypothesis for checking the statistical significance of the difference between two means (μ_1 e μ_2) was done so as to verify the null hypothesis (H_0: $\mu_1=\mu_2$), supposing significance level of 0.01. This test did not rejected the null hypothesis for the following conditions: BW < 2000 g and BW ≥ 2000 g; BW < 2500 g and BW ≥ 2500 g; REDBW < 100000 g.J/cm^2 and REDBW ≥ 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 ≤ BW ≤ 3000 g; BW > 3001 g) did not reject the null hypothesis, since test $F = 0.593308 < F_{tab(2.87)} = 4.857782$.

IV. Discussion

Data acquired in this research, grouped by periods, are difficult to be compared with literature. This is due to methodological differences: the adoption different levels of bilirubinaemia for eligibility to phototherapy, different spectral radiance measurements and different phototherapy techniques. Anyhow, our results are in accordance with current literature regarding the pronounced decrement of TSB in the first 24 hours of treatment.

All fluorescent lamps were changed after approximately 100 hours of use, according to what is currently recommended [6]. It was observed that lamps deteriorate faster than expected under normal conditions, possibly due to its quality. This fact strongly suggests the need for a continuous monitoring of irradiance in phototherapy of the newborn, so as to assure efficacy of the treatment. For all 90 newborns included in the protocol, all irradiance measurements were higher than the minimum established (4 μW/cm^2/nm). The average spectral irradiance, until the end of observation was 4.58 ± 0.31 μW/cm^2/nm.

ANOVA analysis demonstrated that the obtained model using independent variables BW, TSB_1 and REDBW has statistical significance ($p < 0.01$) and also, the *t*–test showed that all variables are significant.

The R^2 found was very close to the corresponding corrected R^2, thus suggesting that the number of samples and the number of variables were adequate for using the least squares fitting method. All the variance inflation factors (VIF) were lower than 5. This fact eliminates the possibility of multicolinearity in data. Analysis of residues indicates that the main underlying assumptions of the regression model were satisfied.

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

V. CONCLUSIONS

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% and shows a gain of 77% (prediction efficiency index) over the prediction using only the average values of TSB_t . 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, thus 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_t, by knowing newborn's BW, TSB at the beginning of phototherapy, the duration of exposition to phototherapy, and the irradiance. Besides, one can infer the time necessary for a given decrement of TSB, under approximately constant irradiance.

A further consideration can be drawn from this research. When a different TSB was obtained, relative to the model's predicted value, there is a clear indication that phototherapy is not properly done. Provided the minimal level of irradiance is assured throughout treatment, possible causes of significant differences between predicted and obtained values of TSB are: incorrect position of the patient regarding the lamps' position, insufficient exposition area (obstructed by cloth, for instance), or particular clinical conditions, initially underestimated or unknown. On the other hand, obtaining TSB decrements that follow the predicted model can reduce the number of blood samples necessary to the clinical control of hyperbilirubinaemia, therefore minimizing discomfort and risks to the newborn.

Future work will include a multicenter prospective study, aiming to confirm the validity and usefulness of the proposed predictive model for the phototherapy of the newborn.

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