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Systematic follow-up of hyperbilirubinemia in neonates with a gestational age of 35 to 37 weeks

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Abstract

Objectives: To determine the outcomes of an intervention for follow-up of bilirubinemia in the first week of life in a cohort of newborn infants with gestational ages between $35^{0/7}$ and $37^{6/7}$ weeks and to determine risk factors for readmission for phototherapy (total bilirubin > 18 mg/dL).

Methods: Retrospective cohort study carried out at a public teaching hospital. Neonates underwent periodic monitoring of total bilirubin levels (measured in plasma or by transcutaneous device) before and after discharge to assess the need for phototherapy. A systematic approach, based on risk percentiles of a bilirubin reference curve, was employed.

Results: The study sample comprised 392 neonates. Only one outpatient visit was required in 61.7% of newborns. Peak total bilirubin was ≥ 20 mg/dL in 34 neonates (8.7%), and reached 25-30 mg/dL in three (0.8%). Phototherapy was indicated after discharge in 74 neonates (18.9%). Weight loss between birth and first follow-up visit and total bilirubin above the 40th percentile at discharge were risk factors for requiring phototherapy. Total bilirubin above the 95th percentile at discharge was associated with greater risk of readmission (RR = 49.5 [6.6-370.3]). Weight loss between discharge and first follow-up visit was the sole independent clinical predictor (RR = 1.16 [1.04-1.17]).

Conclusion: Systematic follow-up during the first week of life was effective in preventing dangerous hyperbilirubinemia. Encouraging breastfeeding and discharging neonates only after weight loss has been stabilized may prevent readmission due to hyperbilirubinemia.

J Pediatr (Rio J). 2011;87(4):301-306: Hyperbilirubinemia, jaundice, premature infant, newborn infant.

Introduction

Preterm neonates are at greater risk of hospital readmission due to hyperbilirubinemia in the first week of life when compared to full-term neonates.[1,2] In premature infants, hyperbilirubinemia is both more prevalent and more severe; serious consequences may arise because neurotoxicity occurs sooner than in full-term newborns, which suggests that prematurity is a significant risk factor for kernicterus.[3]

The best strategy for prevention of severe/hazardous hyperbilirubinemia in neonates with a gestational age of 35 to 38 weeks consists of screening for hyperbilirubinemia in all such newborns at hospital discharge and provision of appropriate outpatient follow-up.[4,5]

There is little information from Brazilian studies on the outcomes of systematic outpatient follow-up of neonates with a gestational week of < 38 weeks in the first week of life.

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Likewise, studies on clinical predictors of hyperbilirubinemia in this particular group of neonates are scarce. Risk factors for hyperbilirubinemia have been determined for full-term and preterm neonates cared for in rooming-in wards.[6,7]

As this information is an essential input for public health actions geared to prevention of hyperbilirubinemia and kernicterus,[8] we believe this description of the outcomes of a dedicated program for outpatient follow-up of hyperbilirubinemia will provide a relevant contribution to the literature.

The present study sought to analyze the outcomes of a program designed to provide systematic follow-up of hyperbilirubinemia in neonates with a gestational age of 35 to 37 weeks and ascertain certain risk factors for readmission due to hyperbilirubinemia.

Patients and methods

This was a retrospective cohort study carried out at a public teaching hospital. The study sample comprised all neonates born between December and July 2008 with a gestational age of $35^{0/7}$ to $37^{6/7}$ weeks who underwent outpatient follow-up of total bilirubin (TB) levels during the first week of life, after discharge from rooming-in, until levels stabilized/declined or phototherapy was indicated. Neonates for whom no data on post-discharge bilirubin levels were available were excluded from the sample, as were those in whom phototherapy was indicated before discharge.

Follow-up of neonatal jaundice at the study institution consisted of two stages. After delivery and prior to discharge, neonates with clinical evidence of jaundice underwent transcutaneous bilirubin (TcB) measurement with a portable device (BiliChek®, Respironics Georgia, Murrysville, USA). If TcB was equal to or greater than 14 mg/dL, total plasmatic bilirubin (TPB) was measured by direct spectrophotometry with a Unistat® bilirubinometer (Leica, Reichert, Buffalo, USA). Infants with early jaundice (TB > 8 mg/dL before the 24th hour of life) were tested for hemolytic disease of the newborn and given phototherapy when necessary. Those with delayed jaundice were followed according to clinical status, with periodical measurement of TB until discharge.

Regardless of previous measurements, on the morning of discharge, all neonates underwent transcutaneous and/or serum bilirubin measurements, obtained with the BiliChek® or Unistat® devices respectively. The former was calibrated before each measurement, and the second, on a daily basis, according to manufacturer instructions. TPB values were plotted onto a reference curve[9] and post-discharge follow-up was recommended for all neonates at at-risk percentiles, regardless of age at discharge. Neonates with TB levels above the 95th percentile were scheduled to return in 24 hours, or remained in the hospital and were reassessed 24 hours later. Neonates with TB levels between the 75th and 95th percentiles returned within 48 hours of discharge, and those with TB values below the 75th percentile, between the 48th and 72nd hours of life.

All neonates were assessed during outpatient follow-up until TB levels declined or stabilized. Follow-up visits were scheduled every 24 to 72 hours depending on bilirubin levels and risk percentiles. Outpatient TB measurements were obtained using the same methods employed for in-hospital assessment. Neonates who missed a follow-up appointment were recalled up to two times before being considered lost to follow-up.

The dependent variable *readmission for phototherapy* was considered present when neonates were readmitted due to hyperbilirubinemia after discharge from the rooming-in ward. The value of TB used to indicate the phototherapy was BTP > 18 mg/dL regardless of time since birth. All neonates admitted with hyperbilirubinemia were treated in double phototherapy units equipped with 14 special blue lamps (Philips® TL52), with a mean spectral irradiance (controlled periodically) exceeding 45 $\mu W/cm^2/nm$.

Information on the independent variables of interest was obtained from a review of follow-up records. The study variables were maternal age and parity, infant gender, gestational age,[10] presence of ABO incompatibility, type of feeding at discharge (exclusive breastfeeding, exclusive formula, or mixed feeding) and hour of life at discharge. ABO incompatibility was considered to be present when the mother had group O blood and the neonate had group A or B blood, regardless of Coombs test results. TcB or TPB were analyzed at discharge and at follow-up, as were peak bilirubin levels during the first week of life and their corresponding percentiles on the reference curve.[9] Weight loss between birth and discharge, weight loss between birth and first follow-up visit, loss to follow-up, and number of follow-up visits were also assessed.

The study was approved by the relevant Research Ethics Committee.

Statistical analysis

The chi-square test was used for comparison of categorical variables according to the presence of readmission for phototherapy. The Mann-Whitney U was used for bivariate analysis of numeric variables after asymmetrical distribution was confirmed by means of the Kolmogorov-Smirnov test. This was followed by univariate and multiple Cox regression analysis, with all variables included in the regression model. A stepwise procedure was used for variable selection. The significance level was set at $p < 0.05$. Analyses were performed in the Statistical Analysis System for Windows 9.1.3 software environment (SAS Institute Inc, 2002-2003, Cary, NC, USA).

Results

Over the study period, 1,916 neonates were followed for control of hyperbilirubinemia during the first week of life at an outpatient clinic established for this specific purpose. Data on gestational age was missing for three newborns. A total of 445 newborns (23.2%) had a gestational age of $35^{0/7}$ to $37^{6/7}$ weeks. Three neonates were excluded due to missing data on progression of bilirubin levels, and 50 others (11.3%) were excluded who required phototherapy during their initial hospital stay (after delivery). Therefore, 392 newborns were referred to the clinic for outpatient follow-up; of these, 44 (11.2%) had TB levels ≥ 15 mg/dL at discharge. Eighteen neonates (4.6%) missed a follow-up appointment, but returned after recall. Of the 392 neonates, 242 (61.7%) had only one scheduled follow-up visit, 61 (15.6%) had two appointments, and 89 (22.7%) returned for three or more visits.

Seventy-four newborns (18.9%) were readmitted for phototherapy at some point during the first week of life. Mean peak TB levels and time to peak TB were 20.2±2.2 mg/dL and 125.1±49.5 hours respectively (Table 1). The overall frequency of TB levels equal to or exceeding 12.9, 15, and 20 mg/dL was 59.7, 33.4, and 8.7% respectively.

The distribution of gestational age in the study population was as follows: 209 infants (53.3%) were born at 37 weeks, 114 (29.1%) at 36 weeks, and 69 (17.6%) at 35 weeks. Readmission rates were 26% for infants born at 35 weeks, 14.9% for those born at 36 weeks, and 18.7% for those with a gestational age of 37 weeks (no significant difference; p = 0.172).

Readmission rates were significantly associated with bilirubin percentile at discharge (p = 0.001): above the 95th percentile, 47.6%; between the 75th and 95th percentiles, 24.3%; between the 40th and 75th percentiles, 13.5%; below the 40th percentile, 3.3% (Table 1).

Three neonates (0.8%) had TPB levels between 25 and 30 mg/dL. One was discharged on the 82nd hour of life, with 8% weight loss and a TcB level of 13 mg/dL (40th-75th percentile); no follow-up was arranged. On the 192nd hour of life, the infant was referred back to our clinic for phototherapy by a primary health care unit, with a TPB of 27.0 mg/dL. The two other neonates were discharged

Table 1 - Study variables according to readmission for phototherapy (n = 392)

Variable	Readmitted for phototherapy		p
	Yes (n = 74)	No (n = 318)	
Maternal age (years)	26 (22.0-31.0)	26 (21.0-31.0)	0.501*
Primiparity (n)	40.0	137.0	0.110†
Birth weight (g)	2,825.0 (2,600.0-3,100.0)	2,787.5 (2,490.0-3,135.0)	0.351*
Gestational age (weeks)	37.0 (36.0-37.0)	37.0 (36.0-37.0)	0.506*
Gender (%)‡			
Male-to-female ratio	62.2:37.8	52.8:45.2	0.196†
ABO incompatibility (%)	8.1	17.9	0.034†
Feeding (%)‡			0.136†
Breast	96.0	92.0	
Formula	0	4.7	
Mixed	1.4	2.2	
Time to discharge (hours)	61 (54.0-70.0)	66 (56.0-77.0)	0.033*
TB at discharge (mg/dL)	13.3 (12.1-15.0)	11.8 (9.7-12.9)	< 0.001*
Percentile at discharge (%)§			< 0.001†
> 95th	27.4	6.9	
75th-95th	45.9	33.4	
40th-75th	21.6	32.0	
< 40th	4.0	27.7	
Weight loss, birth to discharge (%)	8.2 (6.5-9.7)	7.9 (6.2-9.3)	0.395*
Weight loss, birth to follow-up (%)	7.9 (5.1-10.3)	5.5 (2.8-7.9)	< 0.001*
Peak TB (mg/dL)	19.7 (18.5-21.4)	12.9 (11.4-14.2)	< 0.001*
Time to peak TB (hours)	113 (97.0-141.0)	101 (64.0-121.0)	< 0.001*

Values expressed as median (interquartile range) or absolute frequency.
TB = total bilirubin.
* Mann-Whitney U.
† Chi-square test.
‡ No data for 6 cases.
§ No data for 1 case in the phototherapy group.

on the 48th and 58th hours of life, with TcB levels of 13.5 (> 95th percentile) and 12.6 mg/dL (75th-95th percentile) respectively, and returned for scheduled follow-up (24 and 48 hours after discharge), with TPB of 27.4 and 26.3 mg/dL. One of the three had G6PD deficiency. All three neonates received phototherapy and did not develop any signs of acute bilirubin encephalopathy.

Significant differences were found between neonates readmitted for phototherapy and those who did not require readmission in terms of ABO incompatibility, weight loss between birth and follow-up, length of hospital stay after birth, TB at discharge, peak TB, and time to peak TB (Table 1).

On univariate regression analysis, the following variables were identified as risk factors for readmission for phototherapy: weight loss between birth and first follow-up visit; and bilirubin percentile on the reference curve, with levels above the 95th percentile associated with the highest relative risk (RR 14.44, p < 0.001) (Table 2). Multivariate analysis confirmed weight loss to follow-up and bilirubin percentiles as risk factors, with the following relative risks (95%CI): > 95th percentile, RR 49.5 (6.6-370.3) (p < 0.001); 75th-95th percentile, RR 26.65 (3.6-196.5) (p = 0.001); < 75th percentile, RR 14.4 (1.9-108.6) (p = 0.01) (Table 2). Removal of bilirubin percentiles from the model revealed that, in this study sample, weight loss between birth and first follow-up visit was the only independent predictor of readmission (RR 1.16 [1.04-1.17], p < 0.001). Relative risk increased 16% for every 1% of body weight lost.

Discussion

In the present study of infants with a gestational age of $35^{0/7}$ e $37^{6/7}$ weeks, 18.9% of exclusively breastfed neonates required readmission for phototherapy after hospital discharge (mean age at discharge, 66.5±19.4 hours). Total bilirubin levels above the 40th percentile and weight loss between birth and first outpatient follow-up visit were predictive of readmission.

Table 2 - Univariate and multivariate analysis of readmission for phototherapy (n = 392)

Variable	RR, univariate analysis (95%CI)	p	RR, multivariate analysis (95%CI)
Maternal age (years)	1.01 (0.97-1.04)	0.536	–
Parity			–
0	1.37 (0.79-2.39)	0.269	
1	1.00		
≥ 2	0.90 (0.45-1.78)	0.762	
ABO incompatibility			–
Present	1.00	0.064	
Absent	2.2 (0.96-5.08)		
Gender			–
Male	1.32 (0.83-2.11)	0.246	
Female	1.00		
Gestational age (weeks)			–
35	1.4 (0.80-2.44)	0.240	
36	0.80 (0.45-1.41)	0.440	
37	1.00		
Feeding			–
Breast	1.00		
Formula	0.80 (0.76-1.01)	0.058	
Mixed	0.64 (0.09-4.60)	0.657	
Birth weight (g)	1.00 (0.99-1.00)	0.524	–
Weight loss, birth to discharge (%)	1.04 (0.96-1.13)	0.384	–
Weight loss, birth to follow-up (%)	1.11 (1.05-1.17)	< 0.001	1.1 (1.0-1.2)
Percentile at discharge			
> 95th	14.44 (4.29-48.61)	< 0.001	49.5 (6.6-370.3)
75th-95th	7.37 (2.26-23.98)	< 0.001	26.6 (3.6-196.5)
40th-75th	4.11 (1.20-14.12)	0.025	14.4 (1.9-108.6)
< 40th	1.00		1.00

95%CI = 95% confidence interval; RR = relative risk.

Infants born with a gestational age of 35 to 37 weeks are known to be at higher risk of hyperbilirubinemia than neonates born at 38 weeks or later.[2,11-14] There is little information on follow-up of hyperbilirubinemia during the first week of life and on readmission rates for phototherapy – information which could be used to help structure the care required by these patients. Rates may vary widely depending on the definition of hyperbilirubinemia and on the criteria used for indication of phototherapy, as well as on the presence of other risk factors for high bilirubin levels, such as the prevalence of exclusive breastfeeding and the ethnic makeup of each population.

At the time of writing, this was the first Brazilian study to describe the outcomes of a hospital-based program designed for universal follow-up of neonatal hyperbilirubinemia in a large cohort of infants born with a gestational age of 35 to 37 weeks. Our follow-up strategy was based not only on risk percentiles at discharge, but on gestational age as well, in accordance with recent recommendations.[15,16]

In this study, the overall frequency of hyperbilirubinemia was higher (for all TB levels) than that found in other cohorts of preterm and full-term neonates.[11,14] Despite use of different TB cutoffs than those employed in this sample, other studies have found similar percentages of infants requiring phototherapy in the first week of life and similar rates of readmission for phototherapy.[2,17,18] The most widely used criteria for phototherapy at the present time are those proposed by the American Academy of Pediatrics,[12] which use non-evidence-based TB levels and are primarily the result of expert opinions.[19] At our service, the threshold for phototherapy is a TB level of 18 mg/dL, which is approximately 1 mg/dL above the 95th percentile at the 96th hour of life.[9] It bears stressing that this cutoff is based on the availability of high-intensity phototherapy equipment at our facility, which is able to ensure a rapid and safe decline in bilirubin levels.[19] Only 11.2% of the 392 studied neonates had TB levels ≥ 15 mg/dL at discharge (mean age at discharge, 70 hours) which are already an indication for phototherapy according to American Academy of Pediatrics recommendations.[12] Outpatient reassessment of bilirubin levels or delayed discharge are the two possibilities available for management of these neonates, depending on the cutoff used for indication of phototherapy.

In the sample used for development of the original Bhutani at al. reference curve,[9] 2.2 and 0% of neonates with discharge bilirubin levels in the 40th-75th percentile or < 40th percentile respectively later progressed to the 95th percentile, thus potentially requiring treatment. New predictive models using a combination of the reference curve[9] and gestational age[7,20] and weight loss[7] have proven more accurate in determining hyperbilirubinemia than using the original reference curve alone. Our results corroborate these findings.

In this study, 9.1% of neonates with a discharge TB level below the 75th percentile progressed to hyperbilirubinemia requiring readmission – a higher rate than that described by Keren et al.[7] (4%) for the same gestational age range. This was most likely due to the predominance of exclusive breastfeeding in our sample, whereas fewer than half of neonates in the Keren et al. study were on exclusive breastfeeding.[7] Exclusive breastfeeding, particularly when it is ineffective, can lead to a tenfold risk of TB levels > 17 mg/dL.[21]

Likewise, 3.3% of neonates in the lowest risk group (< 40th percentile) of this sample developed bilirubin levels requiring phototherapy, which stresses the need for post-discharge TB monitoring in all neonates in this gestational age range, regardless of risk percentile – in accordance with the most recent recommendations.[15,16]

The presence of TB levels ≥ 25 mg/dL is a rare event, occurring in as few as 0.15% of births.[11] In this sample of higher-risk neonates, 3 infants had post-discharge TPB levels in the range of 25-30 mg/dL, which are highly concerning in terms of encephalopathy risk.[3] Such marked increases in TB could probably have been prevented by more frequent monitoring of bilirubinemia (every 4 to 24 hours), as has recently been proposed by some experts for neonates with a gestational age of 35 to 37 weeks and bilirubin levels above the 75th percentile at discharge.[15,16] This approach is apparently necessary to achieve optimal reduction of hazardous bilirubin levels and, most probably, to reduce the incidence of kernicterus, although the cost-effectiveness and risk-benefit ratio of such frequent monitoring are still unknown.[22]

The risk factors for requiring phototherapy found in this study have been described previously by other authors as important markers of hyperbilirubinemia in full-term and preterm neonates.[7,14,23] However, we expected infants born at 35 weeks would be at higher risk of readmission than those with a more advanced gestational age, as has been suggested by other authors.[12,24] It is reasonable to assume that the relatively small number of very premature newborns in this sample would have prevented establishment of younger gestational age as a risk factor. Earlier hospital discharge was not associated with hyperbilirubinemia in the present study, although discharge between the 48th and 72nd hour of life can double the odds of readmission when compared to delayed discharge.[1]

Greater weight loss between birth and follow-up was identified as the single most significant risk factor for readmission, and is most likely due to insufficient breastfeeding.[25,26]

The limitations of this study are due to its retrospective chart review design, which precluded access to information that might be associated with the outcome of interest, such as a history of jaundice or phototherapy in the neonate's older siblings or presence of cephalohematoma/bruising.

In conclusion, the hyperbilirubinemia prevention program assessed in this study was effective, with 77% of cases having a successful outcome (outpatient discharge or readmission for phototherapy) after only two follow-up visits. However, there is still room for improvement, with implementation of more frequent bilirubin measurements in neonates above the 75th percentile, in accordance with recent recommendations.[15]

The risk factors for readmission identified in this study were sustained weight loss after discharge and serum bilirubin levels at discharge above the 40th percentile of a reference curve, although 3.3% of neonates below this percentile reached TB levels > 18 mg/dL. These findings suggest that measures such as encouraging breastfeeding and discharging infants only after weight loss has stabilized may prevent severe or hazardous hyperbilirubinemia, particularly when outpatient follow-up is unavailable.

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