Early Human Development 88 (2012) 51–55

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Validation of transcutaneous bilirubin nomogram in identifying neonates not at risk of hyperbilirubinaemia: A prospective, observational, multicenter study

Costantino Romagnoli [a,*], Eloisa Tiberi [a], Giovanni Barone [a], Mario De Curtis [b], Daniela Regoli [b], Piermichele Paolillo [c], Simonetta Picone [c], Stefano Anania [d], Maurizio Finocchi [e], Valentina Cardiello [a], Enrico Zecca [a]

[a] Department of Paediatrics, Division of Neonatology, Policlinico A. Gemelli, Catholic University Sacred Heart, Rome, Italy
[b] Department of Paediatrics, Division of Neonatology, Policlinico Umberto I, "Sapienza" University, Rome, Italy
[c] Division of Neonatology, Casilino General Hospital, Rome, Italy
[d] Division of Neonatology, San Filippo Neri Hospital, Rome, Italy
[e] Division of Neonatology, San Pietro FBF Hospital, Rome, Italy

ARTICLE INFO

Article history:
Received 20 April 2011
Received in revised form 30 June 2011
Accepted 2 July 2011

Keywords:
Transcutaneous bilirubin
Hyperbilirubinaemia
Predictive nomogram
Newborn babies

ABSTRACT

Background: Transcutaneous bilirubin (TcB) measurement is widely used as screening for neonatal hyperbilirubinaemia.
Aims: To prospectively validate TcB measurement using hour-specific nomogram in identifying newborn infants not at risk for severe hyperbilirubinaemia.
Study design: prospective, observational, multicenter.
Subjects: 2167 term and late preterm infants born in 5 neonatal units in the Lazio region of Italy.
Methods: All neonates had simultaneous TcB and total serum bilirubin (TSB) measurements, when jaundice appeared and/or before hospital discharge. TcB and TSB values were plotted on a percentile-based hour-specific transcutaneous nomogram previously developed, to identify the safe percentile able to predict subsequent significant hyperbilirubinaemia defined as serum bilirubin >17 mg/dL or need for phototherapy.
Results: Fifty-five babies (2.5%) developed significant hyperbilirubinaemia. The 50th percentile of our nomogram was able to identify all babies who were at risk of significant hyperbilirubinaemia, but with a high false positive rate. Using the 75th percentile, two false negatives reduced sensitivity in the first 48 hours but we were able to detect all babies at risk after the 48th hour of age. Conclusions: This study demonstrates that the 75th percentile of our TcB nomogram is able to exclude any subsequent severe hyperbilirubinaemia from 48 h of life ahead.

1. Introduction

Early postnatal discharge from hospital, within 48 h after birth, combined with exclusive breast feeding and decreased concern about the clinical importance of toxic potential of bilirubin, has been related with an increase in readmissions for phototherapy to treat severe hyperbilirubinaemia [1] as well as with a re-emergence of kernicterus [2].

In order to assess the risk of developing severe hyperbilirubinaemia the American Academy of Pediatrics (AAP) recommends measurement of total serum bilirubin (TSB) in a predischarge newborn population and plotting the results on an hour specific nomogram (for identification of severe hyperbilirubinaemia) [3,4]. On the other hand, strategies based on risk factors and TSB [5,6] and on TSB determination either in umbilical cord blood [7] or within the first day of life [8] failed to identify all newborn babies at risk for developing severe hyperbilirubinaemia. However, the determination of TSB levels remains an invasive, stressful and time consuming procedure.

The determination of transcutaneous bilirubin (TcB) is frequently used to reduce the measurements of TSB and to assess significant hyperbilirubinaemia in term and late-preterm infants [9–17]. Until now the values of TcB have been used to predict severe hyperbilirubinaemia using TSB nomogram [9,11], while a recent trial attempted to convert pre-test predictive ability into post-test predictivity of TcB measurements [18]. In 2008 we constructed a nomogram based on skin bilirubin for the first 96 h of life in a European normal healthy population, obtained with multiwavelength transcutaneous bilirubinometry from 2198 healthy newborn babies (Table 1) [19].

The aim of this study was to verify the predictive value of our nomogram in identifying a 'safe percentile' below which the baby is not at risk for severe hyperbilirubinaemia.

* Corresponding author at: Department of Paediatrics – Catholic University Sacred Heart, Largo A. Gemelli, 8, 00168 Rome, Italy. Tel.: +39 6 30154786; fax: +39 6 3055301.
E-mail address: cromagnoli@rm.unicatt.it (C. Romagnoli).

0378-3782/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.earlhumdev.2011.07.001

Table 1
Values of TcB corresponding at the 50th, 75th and 90th percentile of the hour-specific nomogram elaborated in our population.

Hrs	50th	75th	90th	Hrs	50th	75th	90th	Hrs	50th	75th	90th
24	6.3	7.8	11.1	49	7.7	10.4	11.9	73	10.0	11.7	13.7
25	6.3	7.8	11.1	50	7.8	10.4	12.0	74	10.0	11.8	13.7
26	6.4	7.8	11.1	51	8.0	10.5	12.0	75	10.1	11.9	13.8
27	6.4	7.9	11.2	52	8.1	10.5	12.0	76	10.1	11.9	13.8
28	6.4	7.9	11.2	53	8.3	10.6	12.1	77	10.2	12.0	13.9
29	6.5	7.9	11.2	54	8.4	10.6	12.1	78	10.2	12.1	13.9
30	6.5	7.9	11.2	55	8.6	10.7	12.3	79	10.3	12.2	14.0
31	6.6	8.1	11.2	56	8.7	10.8	12.5	80	10.4	12.2	14.0
32	6.6	8.4	11.2	57	8.9	11.0	12.8	81	10.5	12.3	14.1
33	6.7	8.6	11.2	58	9.0	11.1	13.0	82	10.5	12.3	14.2
34	6.7	8.8	11.2	59	9.2	11.2	13.2	83	10.6	12.4	14.2
35	6.8	9.1	11.2	60	9.3	11.3	13.4	84	10.7	12.4	14.3
36	6.8	9.3	11.2	61	9.4	11.3	13.4	85	10.7	12.4	14.2
37	6.9	9.4	11.3	62	9.5	11.4	13.4	86	10.8	12.4	14.2
38	7.1	9.5	11.4	63	9.6	11.4	13.5	87	10.8	12.4	14.1
39	7.2	9.7	11.5	64	9.6	11.4	13.5	88	10.8	12.4	14.0
40	7.3	9.8	11.5	65	9.7	11.5	13.5	89	10.9	12.4	14.0
41	7.5	9.9	11.6	66	9.8	11.5	13.5	90	10.9	12.4	13.9
42	7.6	10.0	11.7	67	9.8	11.5	13.5	91	10.9	12.5	13.9
43	7.6	10.1	11.7	68	9.8	11.5	13.5	92	10.9	12.5	13.9
44	7.6	10.1	11.8	69	9.9	11.6	13.6	93	10.9	12.6	13.9
45	7.6	10.2	11.8	70	9.9	11.6	13.6	94	10.9	12.6	13.9
46	7.5	10.2	11.8	71	9.9	11.6	13.6	95	10.9	12.7	13.9
47	7.5	10.3	11.9	72	9.9	11.6	13.6	96	10.9	12.7	13.9
48	7.5	10.3	11.9								

2. Methods

2.1. Study Group

This multicenter prospective study was conducted in the region of Lazio, in Italy, through March to December 2009 involving five neonatal units. The Institutional Board approved this study in each site and all parents signed informed consent. In the study we included newborn babies with gestational age (GA) of ≥35 weeks, based on postmenstrual date and early gestation prenatal sonographic findings. We excluded all sick newborn babies who were admitted to the neonatal intensive care unit and those with severe congenital anomalies. None of the studied babies received a drug therapy except for 0.5–1 mg vitamin K (Konakion, Roche Laboratories, Nutley, NJ, USA) administered intramuscularly or orally soon after their birth. We started feeding at 1 hour of life, followed by breast or bottle feeding every 3 h. No prophylactic intervention for hyperbilirubinaemia was employed. During the study period environmental lighting was constant.

2.2. Measurements of TcB and TSB

The measurement of TcB was performed in newborn babies of three neonatal units if clinically jaundiced and/or just before the discharge from the hospital, while in two units TcB was measured only in jaundiced babies. All determinations were made using BiliCheck™ ([BC] Respironics, Marietta, GA – USA). The BC technology allows the optical densities attributed to bilirubin and other skin pigments to be determined avoiding any interference due to several confounding factors: its principles of operation have been described elsewhere [13,15]. Experienced neonatologists performed measurements of TcB with 5 readings in different points of neonatal forehead. Reading's locations were distanced from the hairline and free of any bruising, nevus, haemangioma or other skin anomalies. All measurements were performed on ambient morning light of the nursery while the infant was in a quiet state. The BC devices were calibrated with a disposable tip before each measurement [16]. A single device was used for all measurements in each neonatal unit. No device failure was noticed. In all newborn babies blood samples (50 μL) for the measurements of TSB were collected by heel stick puncture. Capillary tubes were protected from light exposure and after centrifugation they were assayed with the direct spectrophotometer (Microbilimeter Dual Beam Plus model 11144A73G, Ginevri, Rome, Italy) for 30 min. All measurements of TSB were performed by trained technicians, blind to the value of TcB.

A total of 3241 of paired TcB/TSB determinations was obtained from 2167 newborn babies because 728 babies had more than one TcB/TSB measurements. In detail, 506 newborn babies had 2 measurements, 176 had 3 measurements, and 46 had more than 3 measurements.

2.3. Follow-up of studied newborn babies

In each unit, newborn babies are never discharged before 72 h of age independently from the mode of delivery. All newborn babies with a predischarge TcB value >75th percentile of our nomogram were discharged only after two consecutive decreased TSB values, 12 h apart, making us able to identify the peak TSB level. The newborn infants with pre-discharge TcB level between the 50th and the 75th percentile were discharged and controlled 48 h later for hyperbilirubinaemia (determination of TSB). Parents of infants with TcB <50th percentile were counseled to return to the hospital within 5 days after the discharge from the hospital or earlier if they observed persistent jaundice. The decision to use phototherapy was made by the attending neonatologist according to AAP guidelines. For babies exposed to phototherapy we considered only pre-treatment measurements. All perinatal data were recorded in a single database for each site with a selected log of any event occurring during the study period. Care was taken that the same clinical protocol study, method for sample collection and strategies for patient recruitment were prospectively maintained, so that the data from each unit could be pooled.

2.4. Outcome

In our percentile-based hour-specific nomogram the measurements of TcB were plotted separately by two researchers (CR and EZ) after completion of the study. Significant hyperbilirubinaemia was defined as TSB value >17 mg/dL, or as need for phototherapy treatment according to AAP guidelines.

2.5. Statistical Analysis

We performed a statistical analysis using Student's *t*-test for continuous predictors and Fisher's test for categorical data. We assessed the mean difference between paired TcB and TSB, and calculated the correlation of TSB values to measurements of TcB by the linear regression analysis. We calculated the sensitivity, specificity, positive predictive and negative values plotting TcB data in the 50th, 75th and 90th percentile of our TcB nomogram. Receiver operating characteristic (ROC) curve analysis was performed with SPSS software, which was used to assess the predictive ability of our TcB nomogram.

3. Results

A total of 2167 newborn babies (1137 males and 1030 females) of which 184 (8.5%) late preterm were enrolled in the study (Table 2). Mean gestational age (±SD) was 38.9±1.5 weeks (range: 35–42) and mean birth weight (BW) was 3237±471 g (range: 2000–5090). The majority of babies were Caucasian (90.1%) and 53.5% was born after spontaneous delivery. Exclusive breast feeding was prevalent, but 39.1% of babies received also bottle feeding during their hospital stay. Delayed meconium passage (>24 h of life) was observed in 248 (11.4%) babies and only 127 (5.9%) experienced a weight loss greater