Nomogram for Prediction of the Risk of Neonatal Hyperbilirubinemia, Using Transcutaneous Bilirubin

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Assessing the risk of developing severe hyperbilirubinemia, based on a nomogram has been recommended by the American Academy of Pediatrics[10]. The objectives of this study were: 1) To develop an hour-specific nomogram, using transcutaneous bilirubin level (T_CB, Bilicheck, SpecRx, Inc, Norcross, GA, USA), in Thai newborn infants and 2) To determine the risk zones that will predict the development of severe hyperbilirubinemia.

Three hundred and ninety two (392) healthy neonates, born by C-section, were recruited from November 2003 to May 2004. One hundred and eight (108) infants were excluded from the nomogram development due to hemolytic diseases (ABO incompatibility 51, G6PD deficiency 34, combined ABO incompatibility and G6PD deficiency 3) and requirement of phototherapy (20). Nomogram, using daily hour-specific T_CB for 4 days, of 284 neonates was constructed. Plotting all 392 infants, T_CB on the nomogram, the risk zones in relation to the requirement of phototherapy was determined. The 90th percentile (P90) was designated as high risk track with the sensitivity of 96.9%, specificity 78.8%, positive and negative predictive values 29.1% and 99% respectively, and LR 4.6. P10 was labeled as very low risk track, area between P10-P25 as low risk zone, P25-P90 as intermediate zone with P25-P50 as low intermediate and P50-P90 as high intermediate. In conclusion, an hour-specific T_CB nomogram, can be used to identify the risk of subsequent development of severe hyperbilirubinemia. Recognizing the infant's risk enables awareness of the problem and prompt intervention which should reduce severe hyperbilirubinemia and chance to develop bilirubin encephalopathy.

Keywords: *Nomogram, Jaundice, Hyperbilirubinemia, Transcutaneous bilirubin, Newborn infants*

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Neonatal hyperbilirubinemia, one of the most common problems pediatricians encounter in their clinical practice, remains an issue of interest and debate[1,2]. Although the majority of neonatal jaundice is benign, a small number of hyperbilirubinemia poses a major health problem in term of bilirubin encephalopathy or kernicterus[3]. Factors such as inadequate breast milk intake, imbalance between bilirubin production and conjugation and mutation of the gene encoding bilirubin conjugation have been identified to be associated with hyperbilirubinemia[4-6]. Measurement of serum bilirubin in infants at risk and prompt interventiion are the important steps in preventing hyperbilirubinemia and kernicterus. But how to identify infants at risk and when to obtain serum bilirubin are still a cause for concern. The American Academy of Pediatrics (AAP) published a practice parameter on the management of hyperbilirubinemia in healthy term newborn in 1994[7]. Resurgence of kernicterus, reported in the follwing years, partly questioned the adequacy of this parameter. However, there were also comorbid factors, inappropiate application of the guidelines, lack of adherence and less concerned attitude that might play roles in it[3,8,9]. In 2004, AAP issued a clinical practice guideline focused on reducing the frequency of severe hyperbilirubinemia and bilirubin encephalopathy[10]. It recommended assessing the risk of subsequent hyperbilirubinemia by plotting predischarge total serum

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bilirubin (T_SB) or transcutaneous bilirubin (T_CB) on a nomogram and/or assessment of clinical risk factors. East Asian race and known hemolytic diseases, such as G6PD deficiency, were classified in the major risk factor group[10]. The prevalence of G6PD deficiency in Thai neonates is as high as 11.1% in males and 5.59% in females, while among newborns with jaundice, the rates are 22.1% in males and 10.1% in females[11]. These risk factors might cause some difference from the proposed T_SB based nomogram of AAP. The objectives of the present study were: 1) To develop an hour specific nomogram using T_CB in Thai newborn infants and 2) To identify the percentile that will predict subsequent significant hyperbilirubinemia which requires phototherapy.

Material and Method

The present study was performed in the neonatal unit at King Chulalongkorn Memorial Hospital, Bangkok. Newborn infants, born by C-section, whose birth weight was ≥ 2,500 grams and gestational age ≥ 37 weeks were enrolled in the present study. Exclusion criteria included sick newborns, congenital anomaly, infants of diabetic mothers, infants who had asphyxia, hypothermia, hypoglycemia, polycythemia, concealed hemorrhage, and infants who were discharged before 72 hours of age. Cord blood was collected for assessment of infant's blood type and G6PD activity. Infants' gender, gestational age, type of postnatal feeding, maternal blood types and indication for C-section were recorded.

ABO incompatibility was defined as an infant's blood type A or B with type O mother, regardless of the Coomb's test. Rh isoimmunization was defined as different maternal-infant antigen and positive direct Coomb's test.

T_CB measurement using Bilicheck (SpecRx, Inc, Norcross, GA, USA) was conducted on the forehead of the infant in the supine position. The device was calibrated to a standard reference before each measurement in accordance with the manufacturer's instructions. The probe was placed at the same area on the forehead while 5 consecutive scans were triggered for one average T_CB in mg/dL. The hour-specific age at the time of measurement was recorded and designated in one of the 4-hour periods of the day (6 periods per day). Serial measurement was taken every 24 hours until 3-4 days after birth or until jaundice, determined by T_SB, was severe enough to require phototherapy, whichever condition came first. Criteria to initiate treatment for significant hyperbilirubinemia was in accordance with the Clinical Practice Guideline, developed by our staff and is currently used in clinical practice in the authors' neonatal unit[12] (Table 1). The correlation coefficient between T_CB and T_SB using Pearson Linear Regression Analysis was done in a subset of 154 infants.

T_CB of infants who had blood group incompatibility$_r$ G6PD deficiency and normal infants who required phototherapy were excluded from the data used to develop the nomogram, but were retained for identifying the risk zone.

Written informed consent was obtained from the parents and the study was approved by the Faculty's ethical committee.

Data was analysed using SPSS. Nomogram, using hour-specific T_CB of infants who did not have any potential causes to develop hyperbilirubinemia, plotting on every 4 hour period, 6 periods per day for 4 days were calculated into percentile using quadratic regression. Sensitivity, specificity, positive and negative predictive values and likelihood ratio (LR) of T_CB values at different percentiles were analysed in relation to requirement of phototherapy, which represented significant hyperbilirubinemia. ROC (receiver operator characteristic) curve was developed to identify the ability of each percentile in predicting severe hyperbilirubinemia.

Table 1. Clinical practice guideline: management of hyperbilirubinemia in healthy fullterm infant[1]

Age (hr)	Phototherapy	Double phototherapy	Exchange transfusion if double phototherapy fails	Exchange transfusionplus intensive phototherapy
≤ 24*				
25-48	10-12	≥ 15	≥ 20	≥ 25
49-72	≥ 13	≥ 16	≥ 20	≥ 25
> 72	≥ 15	≥ 17	≥ 25	≥ 25

* abnormal: investigation, phototherapy and repeat T_SB within 4-6 hr

Results

From November 2003 to May 2004, 392 infants, born by C-section, were recruited into the present study. The correlation coefficient between T_CB and T_SB of 154 infants was statistically significant ($r = 0.82$, $p < 0.001$).

One hundred and eight (108) infants were excluded from the development of nomogram because of ABO incompatibility (51), G6PD deficiency (34), combined ABO incompatibility and G6PD deficiency (3) and requirement of phototherapy (20). Nomogram was then developed from T_CB of 284 normal infants (Fig. 1), whose demographic characteristics are shown in Table 2. All infants had combined breast and formula feeding during their hospital stay.

Of all 392 recruited infants, 32 (8.2%) had significant hyperbilirubinemia that phototherapy was employed when T_SB reached the threshold level for treatment. Causes of hyperbilirubinemia are shown in Table 3. Plotting all recuited infants' T_CB on the nomagram, sensitivity, specificity, positive and negative predictive values and the likelihood ratio (LR) of different percentiles were calculated in relation to significant hyperbilrubinemia that required phototherapy (Table 4). T_CB of 31 out of 32 infants who required phototherapy were located above the 90th percentile (P90). The ROC curve, demonstrated the positions of various percentile tracks (Fig. 2), showed P90 at the upper left-hand corner, where sensitivity plus specificity of the test were the most. P90 was then deter-

Table 2. Demographic characteristics of normal infants (for nomogram)

Total (284 cases)	N (%)
Male:female	1.1:1
Gestational age (wk)	38.62±1.21
Indication for C-section	
- CPD	113 (39.8)
- repeated C-section	111 (39.1)
- breech presentation	22 (7.7)
- PROM	9 (3.2)
- primigravida	7 (2.5)
- fetal distress	4 (1.4)
- others	18 (6.3)
Feeding:combined breast and formula	284 (100)

Table 3. Causes of hyperbilirubinemia that required phototherapy

Causes (N)	No. of phototherapy (%)
ABO incompatibility (51)	7 (13.7)
G6PD deficiency (34)	5 (14.7)
Combined ABO incompatibility and G6PD deficiency(3)	0 (0)
Unidentified cause in normal infants (304)	20 (6.6)

Table 4. Sensitivity, specificity, positive and negative predictive values (PV) and likelihood ratio (LR) of various percentiles in relation to severe hyperbilirubinemia that required phototherapy

Percentiles	Sensitivity	Specificity	Positive PV	Negative PV	LR
95	75.0	89.4	38.7	82.0	7.1
90	96.9	78.8	29.1	99.0	4.6
85	100.0	57.2	21.3	100.0	3.1
75	100.0	48.3	14.7	100.0	1.9
50	100.0	24.4	10.5	100.0	1.3
25	100.0	5.0	8.6	100.0	1.1
10	100.0	5.0	8.6	100.0	1.0

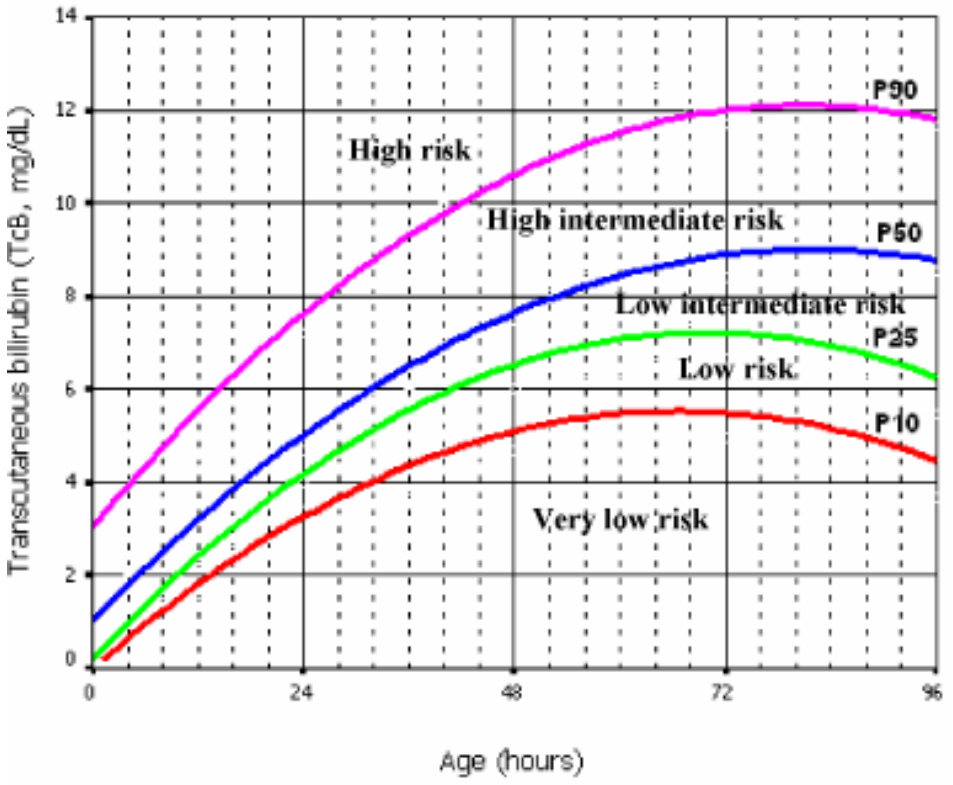

Fig. 1 Nomogram for designation of risk zones, based on hour specific transcutaneous bilirubin levels

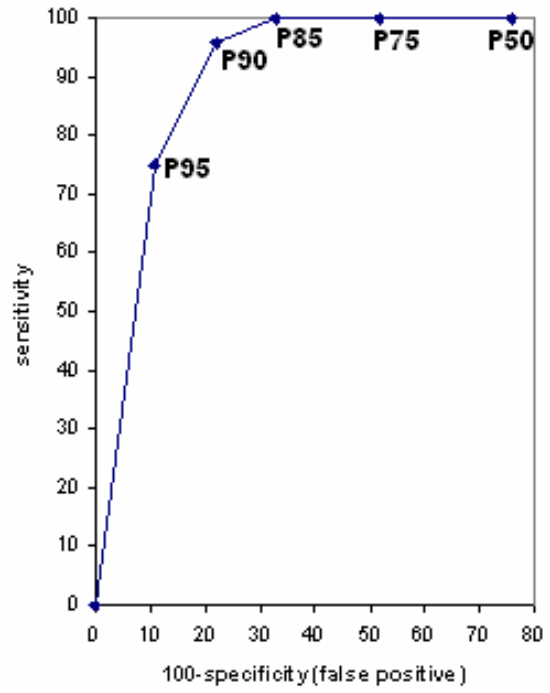

Fig. 2 ROC Curve of various percentiles

mined as high risk track with the sensitivity of 96.9%, specificity of 78.8%, positive and negative values of 29.1% and 99% respectively and LR 4.6. T_CB of P90 were 7.6, 10.6, 12.0 and 11.8 mg/dL at 24, 48, 72 and 96 hours respectively.

All T_CB from the first 24 hours were tracked to identify the subsequent rising to the high risk zone (above P90). It revealed that 58.3% of the infants whose initial T_CB were above P90 remained in the same high risk zone, while 51.8 % of P50-P90, 15% of P25-P50, 8.2% of P10-P25 and 3.4% of < P10 moved upward above P90 (Table 5). There was no infant below P5. P10 was then defined as very low risk track with T_CB of 3.2, 5.0, 5.5 and 4.5 mg/dL at 24, 48, 72 and 96 hours respectively. Area between P10 and P25 was labeled as low risk zone, P25-P90 as intermediate with P25-P50 as low intermediate, and P50–P90 as high intermediate (Fig. 2).

Discussion

Recognizing jaundice visually and deciding whether it is severe enough to warrant blood sampling for T_SB is a difficult judgment for inexperienced health personnel. Doing it whenever in doubt will subject more

Table 5. Numbers and percentages of infants whose T_CB rose above the high risk zone

Percentiles at 24 hours (N)	Subsequent TCB that rose above P90	
	N	%
> P90 (36)	21	58.3
P50-P90 (158)	82	51.9
P25-P50 (120)	18	15.0
P10-P25 (49)	4	8.2
< P10 (29)	1	3.4

than necessary a number of infants to a painful and not without complication procedure. On the other hand, missing one might cause delayed treatment and/or subsequent developing encephalopathy. Transcutaneous measurement of the bilirubin level is easy and safe. Several studies have identified its accuracy and usefulness[13-16]. Because of its noninvasive technique, health personnel are not reluctant to perform it, therefore missing significant hyperbilirubinemia is less likely to happen.

AAP has recommended predischarge assessment of the risk of developing severe hyperbilirubinemia by plotting the result of T_SB or T_CB on a nomogram. Due to the different ethnic origin, prevalence of G6PD in Thai infants, culture, life style and health care delivery system, it is believed that risk demarcations of Thai infants may be different from those of AAP nomogram. As seen in the present study, P90 and P10 were determined as the high and very low risk tracks respectively.

Hour specific T_CB can be easily conducted on the infant at any age to identify the risk zone. P90 has the greatest ability in predicting infants at high risk of having severe jaundice with requirement of phototherapy. Infants who belong in this risk zone might need to be monitored in the hospital to assure that treatment is initiated in time or that subsequent T_CB moves downward into the lower risk zone before discharge.

Infants in the intermediate zone (P25-P90) need to be followed closely, as 16.4 % of the infants in this zone had rising T_CB that moved upward above P90.

Infants in the low risk zone (P10-P25) and very low risk zone (< P10) could be discharged with less concern and flexible schedule for follow up. However, clinical risk factors (AAP)[10] should be taken into consideration the time appropriate for post discharge check up. Although all the infants in the present study had combined breast and formula feeding during their hospital stay, a substantial amount of exclusive breast feeding was practiced after discharge. Breastfeeding was held responsible for 3.6% of being the cause of hyperbilirubinemia that necessitated exchange transfusion[17]. Poor caloric intake and/or dehydration associated with inadequate breast feeding may contribute to the development of hyperbilirubinemia[10]. Therefore, infants with these clinical risk factors have a cause for concern and follow up schedule should be individualized, even if they are placed in low risk in the nomogram.

Although instruction about jaundice is given to all parents before discharge, the significance of severe hyperbilirubinemia might not be fully appreciated if jaundice has not yet become apparent, such as, in infants who are discharged before 48-72 hours or some of the G6PD deficiency who develop jaundice late at the end of the first week[11]. Risk assessment using hour specific nomogram would definitely increase the awareness and emphasize the importance of follow up for both parents and health personnel.

The limitation of the present study is the small number of infants with significant jaundice used to define the risk zone and that T_CB was performed up until 4 days of age only. A larger number of subjects and longer period of T_CB, e.g., until the end of the first week, may be needed to confirm the result.

Conclusion

An hour-specific T_CB nomogram, can be used to identify the risk of subsequent development of hyperbilirubinemia. The percentile distributed risk zones are designated as: high risk > P90, intermediate risk P25-P90, low risk P10-P25 and very low risk < P10. Identifying infants into risk zones enables awareness of the problem and prompt intervention which should reduce severe hyperbilirubinemia and the chance to develop bilirubin encephalopathy.

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การใช้ nomogram ในการทำนายความเสี่ยงต่อการเกิดภาวะ hyperbilirubinemia โดยการวัดระดับ bilirubin ทางผิวหนัง

สุวิมล สรรพวัฒน์, อิศรางค์ นุชประยูร, ชุติมา สมรรคนี, รพีพรรณ หาญสืบสาย

American Academy of Pediatrics ให้แนวทางการดูแลรักษาภาวะตัวเหลืองในทารกแรกเกิด โดยแนะนำให้หาระดับความเสี่ยงต่อการเกิด hyperbilirubinemia จาก nomogram วัตถุประสงค์ของการศึกษานี้คือ 1) สร้าง nomogram จากระดับ bilirubin ที่วัดทางผิวหนัง ($T_C^{\circ}B$) ที่อายุเป็นชั่วโมง และ2) กำหนดความเสี่ยง ที่จะทำนายการเกิดภาวะ hyperbilirubinemia อย่างรุนแรง จากเส้นกราฟใน nomogram ระหว่างเดือนพฤศจิกายน พ.ศ. 2546 ถึงเดือนพฤษภาคม พ.ศ. 2547 มีทารกที่คลอดโดยวิธี C-section จำนวน 392 ราย ทารก 108 รายถูกคัดออก จากการนำไปสร้าง nomogram เนื่องจากมี hemolytic diseases (ABO incompatibility 51 ราย, G6PD deficiency 34 ราย, ABO incompatibility และ G6PD deficiency 3 ราย) และทารก 20 รายที่ได้รับการรักษาด้วย phototherapy การสร้าง nomogram จึงใช้ค่า $T_C^{\circ}B$ ซึ่งวัดที่อายุเป็นชั่วโมงและวัดวันละครั้ง ทุกวันเป็นเวลา 4 วัน จากทารกจำนวน 284 ราย เมื่อนำ $T_C^{\circ}B$ ของทารกทั้งหมด 392 ราย มาลงใน nomogram และตรวจดูความสัมพันธ์ของ percentiles ต่าง ๆ กับภาวะตัวเหลืองที่ต้องรักษาโดยใช้ phototherapy พบว่า percentile ที่ 90 (P90) เป็นระดับที่มีความเสี่ยงสูงโดยมี sensitivity 96.9%, specificity 78.8%, positive และ negative predictive values 29.1 and 99 % ตามลำดับ,และ likelihood ratio 4.6 . P10 เป็น percentile ที่มีความเสี่ยงน้อยมาก โซนที่มีความเสี่ยงน้อยกำหนดที่ P10-P25 ความเสี่ยงปานกลางที่ P25-P90 โดยมี P25-P50 เป็นความเสี่ยงปานกลางค่อนข้างต่ำ และ P50-P90 เป็นความเสี่ยงปานกลางค่อนข้างสูง โดยสรุป การใช้ nomogram โดยเทียบ $T_C^{\circ}B$ ของอายุที่วัดเป็นชั่วโมงบน percentiles สามารถบอกระดับความเสี่ยงของทารกที่จะเกิดภาวะ hyperbilirubinemia ได้ การทราบความเสี่ยงของทารกทำให้เกิดการตระหนักถึงปัญหานี้และให้การรักษาได้ทันท่วงที อันจะนำไปสู่การลดภาวะ hyperbilirubinemia ที่รุนแรงและโอกาสที่จะเกิด bilirubin encephalopathy