RESEARCH PAPER

Transcutaneous Bilirubin Nomogram for Healthy Term and Late Preterm Neonates in First 96 Hours of Life

PARESHKUMAR THAKKAR, HARDAS CHAVDA AND *VIKAS DOSHI

*From Departments of Pediatrics and *Community Medicine, Medical College and SSG Hospital, Vadodara, Gujarat, India. Correspondence to: Dr Pareshkumar Thakkar, 21, Jay Gayatrinagar Society, Near Amitnagar, VIP Road, Vadodara 390 022, Gujarat, India. pareshthakkar@yahoo.com*

Received: March 01, 2016; Initial review: May 19, 2016; Accepted: February 23, 2017.

Objective: To develop nomogram of Transcutaneous Bilirubin among healthy term and late-preterm neonates during first 96 hours of age.

Design: Longitudinal observational study.

Setting: Neonatal unit of a tertiary care Hospital of Central Gujarat, India.

Participants: 1075 healthy term and late preterm neonates (≥35weeks).

Intervention: Six-hourly transcutaneous bilirubin was obtained from birth to 96 hour of life using Drager JM 103 Transcutaneous Bilirubinometer.

Main outcome measures: Nomogram of Transcutaneous Bilirubin with percentile values was obtained, rate of rise of bilirubin was calculated and predictive ability of normative data was analyzed for subsequent need of phototherapy.

Results: The age-specific percentile curves and nomogram were developed from the transcutaneous bilirubin readings of 1,010 neonates. Rate of rise in first 12 hour was 0.2 mg/dL and was 0.17 mg/dL in 12 to 24 hour of life which decreased on second day of life. Neonates who required phototherapy had consistently higher readings of transcutaneous bilirubin and also higher rate of rise in first 48 hrs.

Conclusion: Neonates whose transcutaneous bilirubin is above the 50th percentile should be monitored for the development of significant hyperbilirubinemia.

Keywords: *Hyperbilirubinemia, Jaundice, Prognosis.*

Published online: Match 29, 2017. PII:S097475591600049

It is desirable that after delivery, newborn and mother be discharged as early as possible but the risk of subsequent development of neonatal hyperbilirubinemia is a major hurdle [1,2]. A risk based approach has been advocated by AAP(American Academy of Pediatrics) [3], and by NNF (National Neonatology Forum) of India [4]. However, significant hyperbilirubinemia can also occur in a neonate without any identifiable risk factors. There is a need to have some objective method which can reliably predict the subsequent development of hyperbilirubinemia. The hour specific serum bilirubin nomogram by Bhutani, *et al*. [5] is widely followed, but being invasive is inconvenient for mass screening.

Transcutaneous bilirubin (TcB) measurement being a non-invasive method is feasible for mass screening of at risk neonates. Several studies have reported the utility of TcB as a surrogate of Total Serum Bilirubin (TSB) [6]. TcB nomograms have been published from several countries [7-9], but for Indian population, only one published study is available [10]. The present study was carried out with the objectives of developing TcB nomogram and to assess predictive ability of these nomograms.

METHODS

This was a prospective longitudinal study carried out at Neonatal unit of Department of Pediatrics, Medical College Vadodara, Gujarat over period of 6 months from December, 2013 to June, 2014. The study was approved by scientific review committee and Institutional ethics committee and waiver of consent was granted.

We included healthy term and late-preterm (≥35 weeks) neonates. Exclusion criteria were babies with Rh-isoimmunization, major malformation, hydrops fetalis, first encounter with patient after 1 hour of life, patients who left/ discharged before 48 hours of lifes and NICU admission for >6 hours. Babies who required phototherapy were excluded for construction of nomogram. All newborns, whose mother were Rh-negative or had positive Indirect Coombs test result, were evaluated for blood group and Direct Coombs test results. Neonates who required phototherapy were also evaluated for blood group, Direct Coombs test results and G6PD deficiency.

TcB estimations were done by using Dragger JM – 103, a hand held bilirubinometer that measures TcB levels by using multiwavelength spectral reflectance analysis. All TcB measurements were taken at forehead and we took average of five repeat measurements. All readings were taken with same device by resident doctors, according to the manufacturer's instructions. TcB readings were taken every 6±1 hourly interval starting from 0 hour of life upto 96 hours. After 96 hours of life, whenever possible, we continued to take TcB readings, to know normal change in bilirubin values. The need for phototherapy and management of hyperbilirubinemia was ascertained by treating consultant based on unit protocols and evidence-based practice guidelines of NNF [4]. TSB estimation was done on clinical demand, when TcB values were within 2 mg/dL or 80% of age specific threshold for starting phototherapy (as per nomograms of Bhutani, *et al*. [5]) or when value of TcB was >13 mg/dL.

Discharge and follow up plan was optimized and individualized by a thorough pre-discharge assessment of risk factors for severe jaundice. The institution has a discharge policy of not discharging neonates before 48 hours of age. Neonates who did not return for follow up were telephonically contacted on 14th day of life, to enquire whether the child needed any consultation or admission for any morbidity including jaundice.

Statistical analysis: Baseline and outcome data were recorded in a predesigned performa and master chart was prepared in Microsoft Excel sheet. The data was entered into a custom-designed interface in STATA-IC-13 software and checked for completion, consistency and accuracy. TcB readings were clubbed in 6-hour epochs starting at 0 hour of age. Percentile for each epoch and rate of rise in TcB level in different percentiles were obtained by using same software.

RESULTS

There were 1,782 neonates who were assessed for eligibility; 1,075 neonates were finally included in the study, of which 65 neonates who required phototherapy, were not included for construction of nomogram (***Fig.* 1**).

Of 1010 neonates, gender distribution was almost equal, 28% had weight <2500 grams, 3.9% had gestational age of < 37 weeks and 6.1 % were SGA. All were exclusively breast fed and 969 (95.9%) mothers had received oxytocin during labour.

A total of 12,922 TcB measurements were available in first 96 hours, nomogram of which is shown in ***Fig.* 2**. To follow the normal pattern of bilirubin, 15685 reading were available till 168 hours. Nomogram for this is shown in ***Fig.* 3**.

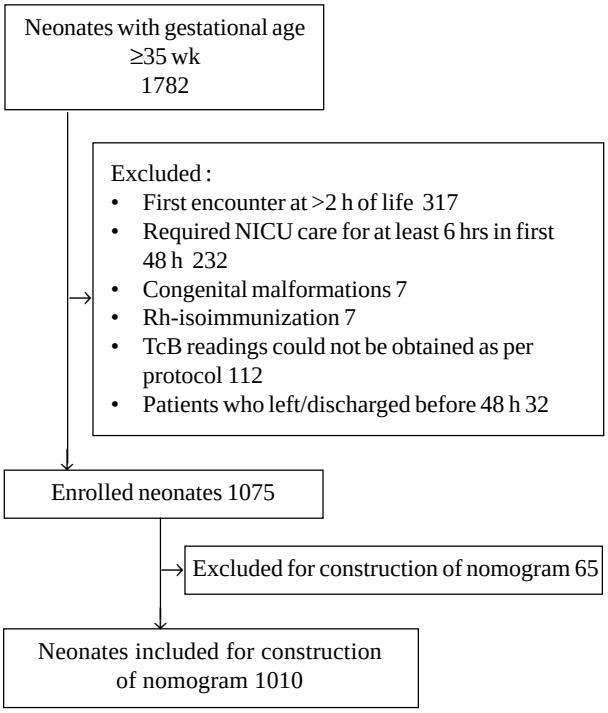

Fig. 1 *Study flow.*

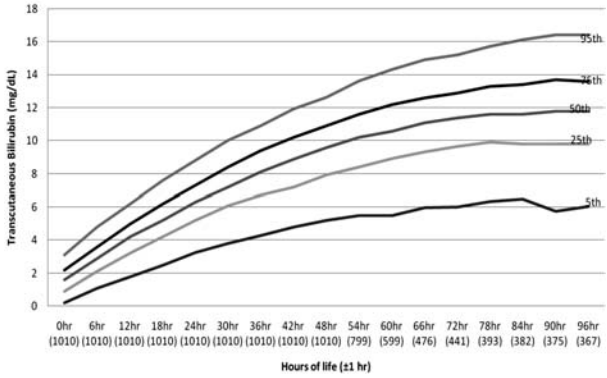

FIG. 2 *Age-specific nomogram of neonates up to 96 hours.*

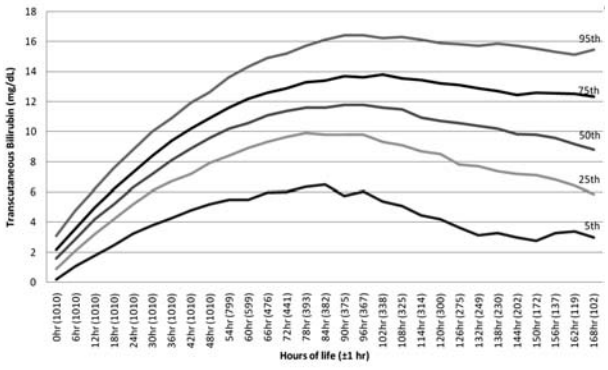

FIG. 3 *Age-specific nomogram of neonates up to 168 hours.*

TcB percentile values are depicted in ***Table* I**. The mean value of TcB at 0 to 1 hour of age obtained was 1.6 mg/dL. Peak value obtained was 11.6 mg/dL at 90 hours of age. The rate of rise (ROR) of TcB percentiles is shown in ***Table* II**. The mean value of ROR observed in first 12 hours of life was 0.2 mg/dL, 0.17 mg/dL at 12 to 24 hours of life, 0.14 mg/dL and 0.12 mg/dL at 24-36 hours and 36 to 48 hours of life, respectively.

Total 65 (6.04%) neonates required phototherapy. The TcB readings were consistently higher in neonates who required phototherapy. The mean TcB value observed at 0-1 hour was 3.08 mg/dL which is between 75th percentile to 95th percentile of the nomogram and they cross a line of 95th percentile at 54 hours with the mean TcB value of 13.76 mg/dL (***Table* I**).

The mean ROR observed in group who required phototherapy was 0.22 mg/dL in first 12 hour compared to 0.2 mg/dL in those who did not. The gap in ROR became wider in 12-24 hours and the fall in ROR was at slower rate in neonates who required phototherapy. So, predictive model based on ROR could be used for early discharge policy if two TcB readings are obtained between 12-48 hours (***Table* II**). The 24hr 50th centile TcB's predictive ability for phototherapy had a sensitivity and negative predictive value of 100% and a specificity of 48.9%. Similarly 50th centile ROR of TcB between 18-24 hour had a sensitivity of 83.1%, negative predictive value of 97.7% and specificity of 47% to predict the need for phototherapy (***Web Table* I**).

TABLE I TCB PERCENTILES

Age in hrs	*TcB values at different percentiles (mg/dL)*				
	5th	*25th*	*50th*	*75th*	*95th*
0	0.2	0.9	1.6	2.2	3.1
6	1.1	2.1	2.9	3.6	4.8
12	1.8	3.2	4.2	5.0	6.2
18	2.5	4.2	5.2	6.2	7.6
24	3.2	5.2	6.3	7.3	8.8
36	4.3	6.7	8.1	9.4	10.9
48	5.2	7.9	9.6	10.9	12.6
60	5.5	8.9	10.6	12.2	14.3
72	6.0	9.6	11.4	12.9	15.2
96	6.0	9.8	11.8	13.6	16.4

TcB = transcutaneous bilirubin.

TABLE II TRANSCUTANEOUS BILIRUBEN RATE OF RISE PERCENTILES FOR NORMAL NEONATES (*N*=1010)

Age in hrs	*TcB rate of rise (mg/dL) percentiles*				
	5th	*25th*	*50th*	*75th*	*95th*
0-6	0.1	0.1	0.2	0.3	0.4
6-12	0.1	0.1	0.2	0.3	0.4
12-18	0.1	0.1	0.2	0.2	0.4
18-24	0	0.1	0.2	0.2	0.4
24-36	0	0.1	0.1	0.2	0.3
36-48	0	0.1	0.1	0.2	0.2
48-60	0	0.1	0.1	0.1	0.2
60-72	0	0.1	0.1	0.1	0.2

TcB = transcutaneous bilirubin.

DISCUSSION

Present study provides normative data with various percentile values of TcB and its rate of rise in term healthy and late preterm Indian neonates. The neonates who required phototherapy had consistently higher readings of TcB and ROR.

Nomograms using TcB have been developed by various countries for their population, but only a single study from India by Mishra, *et al*. [10]. The ROR observed in the study of Mishra, *et al*. [10] is somewhat higher in first 48 hours compared to our study. This may be because there were more pre-term neonates in their study group compared to the present study. Maisels, *et al*. [7] provide nomograms from a predominantly white population from North America from a convenient sample of day time TcB measurements after six hours of life. The overall TcB observations including all percentiles are lower compared to our data. This can be due to almost all newborns in our study were exclusively breastfed and due to racial and ethnic variations. A systemic review by De Luca, *et al*. [11] had compared four TcB nomogram developed in North America (mixed population) [7], European [8], Hispanic [12] and Thai population [9]. The analysis revealed significant differences in values of bilirubin across various populations. Significant differences were observed in TcB values at different percentiles at different hours of life, different rate of rise and peak values of TcB. Nomogram have been also reported from Canada [13,14], Brazil [15], China [16] and Israel [17] for healthy term and late pre-term neonates. The Israel [17] study included only clinically jaundiced neonates. The Brazilian [15] study included only term neonates. Nomogram developed by De Luca, *et al*. [8] had also included neonates who required phototherapy. Few of the authors have given separate nomogram according to gestational age [7]. The major limitation of almost all studies is that they are not population-based and represent data from single center.

There were few limitations of this study. It is not a

WHAT IS ALREADY KNOWN?

- Transcutaneous Bilirubin estimation is non-invasive and useful method for screening of neonates for the risk of development of hyperbilirubinemia.

WHAT THIS STUDY ADDS?

- This study provides transcutaneous bilirubin nomogram for healthy term and late preterm Indian neonates with percentiles and its rate of rise.

population-based study; however, with increasing number of institutional deliveries, our sample of healthy neonates by and large is representative of normal neonatal population. For developing country-wide nomogram, a multicenter trial should be conducted. The nomogram should be validated for predictive ability with a separate cohort of neonates.

The present study provides a nomogram of natural history of bilirubin in healthy term and late pre-term neonates in predominantly breast fed, unselected population. On the basis of this data we conclude that neonates whose TcB is above the 50th percentile at 24 hrs should be closely monitored for development of significant hyperbilirubinemia.

Contributors: PT: conceived and designed the study; HC: was involved in data collection; PT, VD, HC: did analysis and interpretation of data; PT, HC: drafted the manuscript. All authors have approved the final version of manuscript.
Funding: None; *Competing interest*: None stated.

REFERENCES

1. Friedman MA, Spitzer AR. Discharge criteria for the term newborn. Pediatr Clin North Am. 2004;51:599-618.
2. Maisels MJ, Kring E. Length of stay, jaundice, and hospital readmission. Pediatrics. 1998;101:995-8.
3. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114:297-316.
4. Thakre R, Murki S, Venkataseshan S. Management of Neonatal Hyperbilirubinemia. *In*: Evidence Based Clinical Practice Guidelines. *eds*. Kumar P, Jain N, Thakre R, Murki S, Venkatasestan. National Neonatology Forum, New Delhi; 2010: p. 139-54.
5. Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. Pediatrics. 1999;103:6-14.
6. Mahajan G, Kaushal RK, Sankhyan N, Sharma RL, Nakra M. Transcutaneous bilirubinometer in assessment of neonatal jaundice in northern India. Indian Pediatr. 2005;42:41-5.
7. Maisels MJ, Kring E. Transcutaneous bilirubin levels in the first 96 hours in a normal newborn population of > or = 35 weeks' gestation. Pediatrics. 2006;117:1169-73.
8. De Luca D, Romagnoli C, Tiberi E, Zuppa AA, Zecca E. Skin bilirubin nomogram for the first 96 h of life in a European normal healthy newborn population, obtained with multiwavelength transcutaneous bilirubinometry. Acta Paediatrica. 2008;97:146-50.
9. Sanpavat S, Nuchprayoon I, Smathakanee C, Hansuebsai R. Nomogram for prediction of the risk of neonatal hyperbilirubinemia, using transcutaneous bilirubin. J Med Assoc Thai. 2005;88:1187-93.
10. Mishra S, Chawla D, Agarwal R, Deorari AK, Paul VK. Transcutaneous bilirubin levels in healthy term and late preterm Indian neonates. Indian J Pediatr. 2010;77:45-50.
11. De Luca D, Jackson GL, Tridente A, Carnielli VP, Engle WD. Transcutaneous bilirubin nomograms: a systematic review of population differences and analysis of bilirubin kinetics. Arch Pediatr Adolesc Med. 2009;163:10.
12. Engle WD, Lai S, Ahmad N, Manning MD, Jackson GL. An hour-specific nomogram for transcutaneous bilirubin values in term and late preterm Hispanic neonates. Am J Perinatol. 2009;26:425-30.
13. Wainer S, Parmar SM, Allegro D, Rabi Y, Lyon ME. Impact of a transcutaneous bilirubinometry program on resource utilization and severe hyperbilirubinemia. Pediatrics. 2012;129:77-86.
14. Wainer S, Rabi Y, Parmar SM, Allegro D, Lyon M. Impact of skin tone on the performance of a transcutaneous jaundice meter. Acta Paediatrica. 2009;98:1909-15.
15. Draque CM, Sanudo A, de Araujo Peres C, de Almeida MF. Transcutaneous bilirubin in exclusively breastfed healthy term newborns upto 12 days of life. Pediatrics. 2011;128:e565-71.
16. Yu ZB, Dong XY, Han SP, Chen YL, Qiu YF, Sha L, *et al*. Transcutaneous bilirubin nomogram for predicting neonatal hyperbilirubinemia in healthy term and late-preterm Chinese infants. Eur J Pediatr. 2011;170:185-91.
17. Bental YA, Shiff Y, Dorsht N, Litig E, Tuval L, Mimouni FB. Bhutani-based nomograms for the prediction of significant hyperbilirubinaemia using transcutaneous measurements of bilirubin. Acta Paediatr.2009;98:1902-8.
18. Yu ZB, Han SP, Chen C. Bilirubin nomograms for identification of neonatal hyperbilirubinemia in healthy term and late-preterm infants: a systematic review and meta-analysis. World J Pediatr. 2014;10:211-8.

WEB TABLE I PREDICTIVE ABILITY OF TRANCUTANEOUS BILIRUBIN AND ITS RATE OF RISE FOR SUBSEQUENT NEED OF PHOTOTHERAPY

Situation of TcB at 24 hours of age		*Predictive characteristics*			
Percentile zones (total n=1075)	*Children who required phototherapy (n=65)*	*Sn (%)*	*Sp (%)*	*PPV (%)*	*NPV (%)*
≥95th Percentile (74/1075)	22/65	33.8	94.9	29.7	95.7
≥75th Percentile (327/1075)	58/65	89.2	73.4	17.7	99.1
≥50th Percentile (581/1075)	65/65	100	48.9	11.2	100
≥25th Percentile (838/1075)	65/65	100	23.5	7.8	100
≥5th Percentile (1025/1075)	65/65	100	5	6.3	100
For Rate of Rise of TcB between 18 to 24 hours of life					
≥95th Percentile (44/1075)	5/65	7.7	96.1	11.4	94.2
≥75th Percentile (305/1075)	26/65	40	72.4	8.5	94.9
≥50th Percentile (589/1075)	54/65	83.1	47	9.2	97.7
≥25th Percentile (831/1075)	61/65	93.8	23.8	7.3	98.4
≥5th Percentile (1059/1075)	65/65	100	1.6	6.1	100

TcB= transcutaneous bilirubin, Sn = sensitivity, Sp = specificity, PPV = positive predictive value, NPV = negative predictive value.