

Original Research Article

Endtidal carbonmonoxide and carboxyhemoglobin for prediction of significant hyperbilirubinemia in healthy Indian neonates >35 weeks of gestation

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Received: 01 May 2020

Accepted: 06 May 2020

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ABSTRACT

Background: Endtidal carbonmonoxide (ETCOc) and Carboxyhemoglobin (COHB) levels correlate well to bilirubin production and an availability of non-invasive point of care (POC) device in predicting significant hyperbilirubinemia is of great advantage when compared to measurement of serum bilirubin. Objective of the study is to measure a value of ETCOc and COHB in the early neonatal period for the prediction of significant hyperbilirubinemia.

Methods: This was the descriptive Cross Sectional Study. ETCOc and COHB were measured 12th hourly for 72 hours followed by TSB in whom the TCB was >14mg/dl. Neonates were classified as jaundiced whose TSB values were in phototherapy range as per AAP Recommendations. Receiver Operative Curves (ROC) were created by appropriate statistical software for ETCOc and COHB to predict significant hyperbilirubinemia. The Sensitivity, Specificity, Positive predictive value, Negative predictive value and likelihood ratios of each was determined and the correlation between ETCOc and COHB levels, ETCOc and TCB, COHB and TCB at different hours of age was evaluated.

Results: Among the total 320 infants, 156 of them developed significant hyperbilirubinemia. The ETCOc and COHB level at 60 hours of age was the most predictive of significant hyperbilirubinemia by ROC analysis. ETCOc cut-off of 1.65 ppm at 60 hours of age has a sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio of 84.6%, 80.5%, 80.5% and 84.6%, 4.33 and 0.19. COHB cut-off of 1.32 ppm at 60 hours of age has a sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio of 84.6%, 81%, 80% and 84.2%, 4.34 and 0.19. ETCOc had a maximum correlation with COHB at 48 hours of age.

Conclusions: An increased level of Endtidal carbonmonoxide and Carboxyhemoglobin in the early neonatal period is useful as a screening test for prediction of significant hyperbilirubinemia.

Keywords: Carboxyhemoglobin, Early neonatal period, Endtidal carbonmonoxide corrected, Hyperbilirubinemia

INTRODUCTION

Jaundice is one among the most common conditions requiring medical care in newborn babies. During the first week of life, more than 60% of healthy full term and 80% of preterm newborns develop hyperbilirubinemia.

However, approximately 5% to 10% of neonates develop severe hyperbilirubinemia, defined as having total serum bilirubin (TSB) above 95th centile for age in hours, that requires phototherapy.¹⁻³ Bilirubin production rate can be estimated by measuring the breath Carbonmonoxide levels and Carboxyhemoglobin levels

measured by Masimo Radical-7 monitor. The endtidal carbon monoxide (ETCOc) and Carboxyhemoglobin (COHB) levels correlate well to bilirubin production in neonates in the absence of pulmonary dysfunction. Having a non-invasive point of care (POC) device in predicting significant hyperbilirubinemia is of great advantage when compared to measurement of serum bilirubin by invasive method.

As such there are no Indian studies till date on the measurement of Endtidal carbon monoxide (ETCOc) and Carboxyhemoglobin (COHB) levels by non-invasive method to predict significant hyperbilirubinemia in healthy neonates. This study is designed to estimate the values of ETCOc and COHB in predicting significant hyperbilirubinemia.

METHODS

This descriptive study was conducted from October 2015 to March 2016 in the Intramural unit, Department of Neonatology, Madras Medical College, Chennai after obtaining clearance from the Institutional Ethics Committee. Sample size was calculated with Sensitivity of ETCOc and COHb in previous study (Okuyama et al.) of 86%. Precision (d) kept as 5%. By using $(4PQ/d^2 \times \text{Prevalence})$ formula minimum required sample is 320, where $P = \text{Sensitivity}$, $Q = 100 - P$. Subjects were recruited from amongst the live born infants delivered in Institute of Obstetrics and Gynaecology.

Inclusion criteria

- Gestational age more than 35 weeks.
- Appropriate for Gestational age and Small for gestational age babies.
- Enrolled in the study in first 12 hrs of life.

Exclusion criteria

- Neonates with major congenital malformations.
- Neonates requiring NICU admission.
- Neonates born to mothers with H/o. maternal smoking.

Parents of subjects who satisfy eligibility criteria were approached for participation in the study and were provided information about the study. After obtaining written informed consent from a parent, the baby was enrolled. Endtidal carbon monoxide (ETCOc) and Carboxyhemoglobin (COHb) levels of all babies who met the inclusion criteria were measured every 12 hrs during the first 72 hrs of life in healthy, Indian infants >35 week of gestation using a breath carbon monoxide analyzer (PICO⁺) and Masimo monitor. In this study, the endtidal carbon monoxide was measured using a mask fitted to the carbon monoxide breath analyzer and carboxyhemoglobin (COHB) was measured non-invasively using Masimo radical-7 monitor. Bilirubin will be measured by Transcutaneous bilirubinometer (TCB) in

babies at 24, 48, 72, 120 hrs and day 7 of life. Under strict aseptic precautions blood samples for TSB will be collected by venepuncture in babies whose TCB values are more than 14mg/dl.

Neonates who develop significant jaundice requiring phototherapy as per AAP Guidelines will be included in the test while, Neonates will be qualified as control subjects if their TSB levels were not in phototherapy range as per AAP recommendations.

Measurement

Endtidal carbon monoxide determination will be done with PICO⁺ carbon monoxide breath analyzer, a hand-held portable device and Carboxyhemoglobin values will be measured by non-invasive method using Masimo Radical-7 monitor. All measurement were performed with the same device by investigator according to the manufacturer's instructions and the standard described technique. The ETCOc and COHb values of Hyperbilirubinemic babies at which phototherapy is initiated was assessed for the prediction of significant hyperbilirubinemia.

Laboratory measures

Blood will be collected by venepuncture in babies who develop significant jaundice requiring phototherapy. The bilirubin estimation was done by Photospectrometric bilirubin analyzer (Bili-Micro Meter, Kohsoku Denki Co Ltd, Tokyo, Japan). The micro-capillary tube containing the blood sample was blocked at one end and centrifuged at 12000 rpm for 5 minutes in a micro centrifuge to separate the serum. The processed micro capillary tube was fixed on to the holder of spectrometric bilirubin analyzer ensuring the serum column covered the entered length of the slit through which the light passes. A microprocessor converts the light intensity received by photodetector into the total bilirubin value which is digitally displayed. This method for estimation of bilirubin is simple, requires no reagents and needs only 50-70 µL of blood.

Statistical analysis

Data was recorded in a predesigned Performa analysed with appropriate statistical methods and percentile curves was drawn for observed values. Percentile charts and Receiver Operative Characteristic (ROC) curve was created by appropriate statistical software for ETCOc and COHb levels to predict significant hyperbilirubinemia. The Sensitivity, Specificity, Positive predictive value, Negative predictive value and likelihood ratios of each was determined.

The ROC curves of ETCOc and COHB at different ages between 12 to 72 hrs after birth was constructed and an optimal cut-off point was chosen by determining the nearest point on the ROC Curve to the left upper corner,

where the expected benefit is maximum. The correlation coefficient between ETCOc and COHb levels, ETCOc and TCB, COHB and TCB at different hours of life was evaluated.

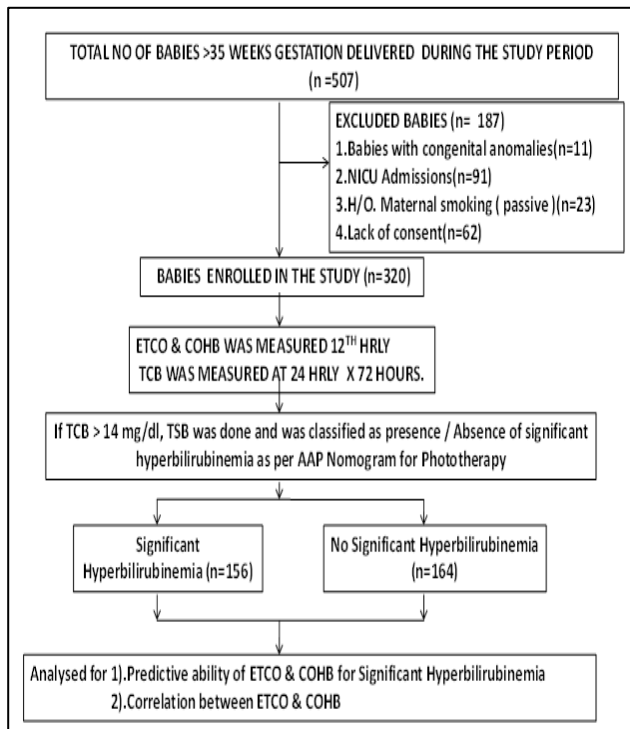


Figure 1: Flow of participants.

RESULTS

Among the neonates delivered during the study period, 507 babies met the eligibility criteria. Of them, 187 babies were excluded. Out of excluded babies, ninety one neonates were admitted in NICU; eleven of them

were born with congenital anomalies and twenty three of them were excluded as there was h/o passive maternal smoking. Sixty two babies were excluded in view of denial of consent (Figure 1).

Finally 320 neonates were enrolled in the study. 156 neonates developed jaundice and 164 of them did not develop significant jaundice. None of the subjects were lost to follow up and data of all 320 subjects were collected and analyzed.

Description of baseline characteristics

The demographic profile and baseline maternal characteristics are summarized. 66 (20.6%) of the mothers had gestational diabetes mellitus and 41 (12.8%) of them had pregnancy induced hypertension. Oxytocin was used to augment labour in 11.5% mothers (37/320). Nearly half of the mothers were primigravida (50.9%) (163/320).

Males constituted 52.8% (169/320). 257 (80.3%) neonates were born by caesarean section and the remainder (n=63) by vaginal route (19.7%). 42 subjects were between 35 to 37 weeks of gestation which constituted around 13.1%. The birth weight of vast majority babies in the study group were between 2500 to 2999 grams.

Comparison of baseline variables in both groups

The baseline variables were balanced among the two groups. There was no statistical difference between jaundiced and non-jaundiced babies regarding gestational age (p value=0.58); birth weight (p value=0.54), sex ratio (p value=0.55) and Mode of delivery (vaginal: 21.2 vs. 18.3 % respectively, cesarean section: 78.8% vs. 81.7% respectively) (Table 1).

Table 1: Baseline neonatal characteristics.

Parameters		Total no of babies (N=320) n (%)	Significant hyperbilirubinemia (N=156) n (%)	No significant hyperbilirubinemia (N=164) n (%)	p-value
Gestation (weeks)	35 to <37	42 (13.1)	20 (12.8)	22 (13.4)	0.58
	37 to 42	278 (86.9)	136 (87.2)	142 (86.6)	0.34
	Mean gestation	38+3 (±1.4)	38+4 (±1.3)	38+3 (±1.4)	0.75
Birth weight (grams)	2000 - 2499	36 (11.2)	21 (13.4)	15 (9.1)	0.54
	2500 - 2999	164 (51.2)	81 (51.9)	83 (50.6)	
	3000 - 3499	101 (31.5)	44 (28.2)	57 (34.7)	
	3500 - 3999	16 (5)	9 (5.8)	7 (4.2)	
	>4000	3 (1.1)	1 (0.7)	2 (1.4)	
	Mean birth weight	2.91 (±0.36)	2.87 (±0.35)	2.94 (±0.36)	0.07
Sex	Boys	169 (52.8)	85 (54.4)	84 (51.2)	0.55
	Girls	151 (47.2)	71 (45.6)	80 (48.8)	
Mode of delivery	LSCS	257 (80.3)	123 (78.8)	134 (81.7)	0.52
	LN	63 (19.7)	33 (21.2)	30 (18.3)	

Table 2: Risk factors for neonatal hyperbilirubinemia.

Parameters	Total no of babies (N=320) n (%)	Significant hyperbilirubinemia (N=156) n (%)	No significant hyperbilirubinemia (N=164) n (%)	p-value
Late preterm (35-37 weeks)	42(13.1)	20(12.8)	22(13.4)	0.580
Cephalhematoma	38(11.8)	27(17.3)	11(6.7)	0.003
Bruising	26(8.1)	20(12.8)	6(3.6)	0.003
Cephalhematoma and bruising	15(4.7)	15(9.6)	0(0)	<0.001
ABO Incompatibility setting	81(25.3)	47 (30.1)	34(20.7)	0.149
Rh Incompatibility setting	26(8.1)	20(12.8)	6(3.6)	0.006
H/O Jaundice in previous sibling	77(24)	56(35.8)	21(12.8)	<0.001

Table 3: Cut-off values, sensitivity, specificity, PPV, NPV and LR for ETCOc at different postnatal ages.

Age (hrs)	Cut off value (ppm)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR-
12	0.55	68.6	81.7	78.1	73.2	3.74	0.38
24	0.65	73.1	30.5	50	54.3	1.05	0.88
36	1.15	61.5	66.5	63.6	64.5	1.83	0.57
48	1.25	85.3	40.9	57.8	74.4	1.43	0.35
60	1.65	84.6	80.5	80.5	84.6	4.33	0.19
72	1.65	91.7	57.9	67.5	88	2.17	0.14

Table 4: Cut-off values, sensitivity, specificity, PPV, NPV and LR for COHB at different postnatal ages.

Age (hrs)	Cutoff value (p.p.m)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR-
12	0.36	84.6	41.5	57.9	73.9	1.44	0.37
24	0.52	73.1	30.5	50	54.3	1.05	0.88
36	0.76	68.6	28	47.6	48.4	0.95	0.43
48	1.08	69.9	54.9	59.6	65.7	1.54	0.54
60	1.32	84.6	81	80	84.2	4.34	0.19
72	1.32	91.7	57.9	67.5	88	2.18	0.14

The common risk factors for jaundice like cephalhematoma, bruising, ABO incompatibility, Rh incompatibility and h/o jaundice in the previous sibling were evaluated. 17.3% (27/156) of subjects with cephalhematoma and 12.8% (20/156) of subjects with bruising developed significant jaundice ($p < 0.003$). When both the risk factors (cephalhematoma and bruising) were present, the risk for subsequent jaundice was 100%, with a highly significant (p value < 0.001). 12.8% (20/156) who developed jaundice were Rh incompatibility subjects ($p = 0.006$) and H/o. jaundice in previous sibling was a major risk factor development of jaundice ($p < 0.001$) (Table 2).

Prediction of significant hyperbilirubinemia

The ROC Curve for Endtidal carbon monoxide at 60 hours of age has a maximum area under curve of 0.87 (CI: 0.83-0.91) with a cut-off value of 1.65 ppm at 60 hours of age (Figure 2). The sensitivity, specificity, Positive predictive value and Negative predictive value

were 84.6%, 80.5%, 80.5% and 84.6% (Table 3).

Similarly, the ROC curve for Carboxyhemoglobin measurements showed a maximum area under curve 0.87 (CI: 0.83-0.91). At a cut-off value of 1.32 ppm at 60 hours of life (Figure 3). The sensitivity, Specificity, Positive predictive value and Negative predictive value was 84.6%, 81%, 80% and 84.2%. The positive and Negative Likelihood ratio was 4.34 and 0.19 (Table 4).

Correlation between ETCOC, COHB and TCB

Endtidal Carbon monoxide was found to correlate well with Carboxyhemoglobin at different postnatal ages with correlation co-efficient of 0.99 and highly significant p value ($p < 0.001$). Correlation between endtidal carbon monoxide and carboxyhemoglobin is best at 48 hours of age. Correlation between endtidal carbon monoxide (ETCOC) and Transcutaneous bilirubin (TCB) is best at 72 hours of age with correlation co-efficient of 0.64 and a highly significant (p value

<0.001). The Correlation co-efficient between Carboxyhemoglobin (COHB) and Transcutaneous bilirubin (TCB) is 0.63 and best at 72 hours of age with a highly significant (p value <0.001).

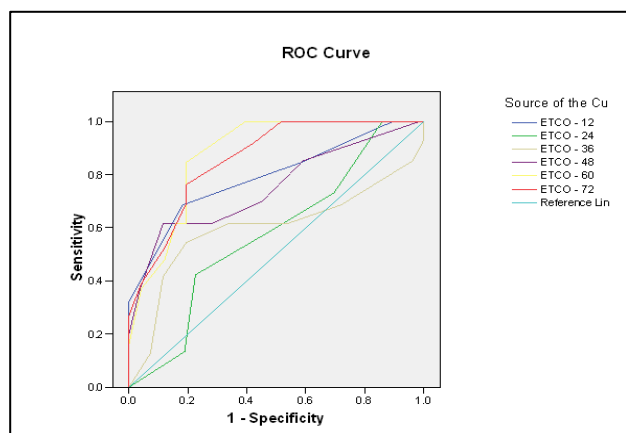


Figure 2: ROC curve for ETCOc for different hours.

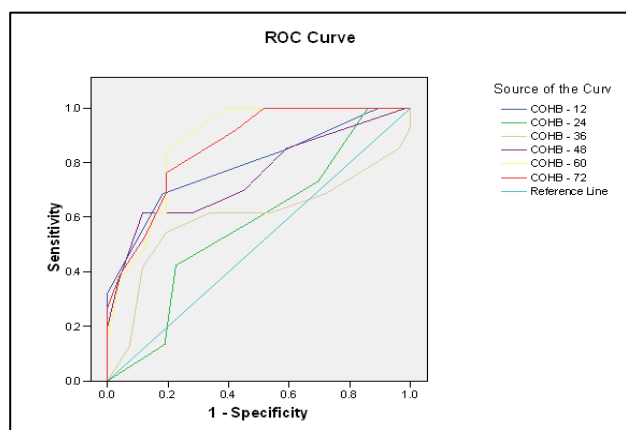


Figure 3: ROC curve for COHB for different hours.

DISCUSSION

Three hundred and twenty neonates >35 weeks of gestation were enrolled in the study within twelve hours of age and were followed up for the next 72 hours. A value of endtidal carbonmonoxide and carboxyhemoglobin at 60 hours of age was the best in prediction of significant hyperbilirubinemia. Correlation between ETCOc and COHB measurements were maximum at 48 hours of age.

Endogenous production of carbonmonoxide have been measured with various methods since 1940s. Engel et al, have found an excellent correlation between endogenous production of carbonmonoxide and bilirubin production.⁴ Carbonmonoxide (CO) and biliverdin are produced in equimolar amounts and biliverdin is quantitatively reduced to bilirubin.⁵ The measurement of carbonmonoxide in breath or blood can be used as an index of heme degradation and bilirubin production.⁶ Studies conducted by National Institute of Child Health

and Human Development (NICHD) demonstrate the feasibility of estimating bilirubin production as measured by Carbonmonoxide in breath.^{7,8} Elevated levels of exhaled carbonmonoxide may be helpful in identifying infants who are producing large amounts of bilirubin via a hemolytic process. Endtidal carbonmonoxide measurement may be of limited value in neonates whose mother smoked during pregnancy as the fetus receives exogenous carbonmonoxide through the placenta.⁹ After birth the neonate exhales carbonmonoxide which may cause false positive readings.

The endtidal carbonmonoxide measurements have been shown to correlate well with pulmonary excretion of carbonmonoxide.¹⁰ Therefore, determination of endtidal carbonmonoxide is preferred, because it is non-invasive, immediate, accurate and reliable when compared to other methods.

This study was conducted in a tertiary care maternity hospital in a developing country, which accounts to an annual delivery rate of fifteen thousand neonates. The prevalence of jaundice in this unit is 50-60 % in >35 weeks of gestation. This rate is comparable to the ones reported by most authors in literature, both across the country and beyond. The risk factors that cause jaundice in this unit resemble those widely reported in standard textbooks and in the published literature. Hence, authors expect that this results would be generalizable to other units.

There was no statistical significance between type of delivery, gestation, sex and development of significant hyperbilirubinemia. 71% of babies with cephalhematoma and 76.9% of babies with bruising developed significant hyperbilirubinemia (p value 0.003). When both the risk factors (cephalhematoma and bruising) were present in the same baby, then all babies (100%) developed jaundice with a highly significant p value (0.001). Rh negative setting was found to be a significant risk factor for development of jaundice (p value 0.006). In a similar study done by Uetani et al, he demonstrated that the endtidal carbonmonoxide values were significantly higher in babies who developed neonatal jaundice as a result of ABO incompatibility or Rh incompatibility.¹¹

ROC curve analysis

In Okuyama et al, study endtidal carbonmonoxide values were measured every 6th hourly during the first 72 hours of life.¹² The endtidal carbonmonoxide values at 42 hours of life was best in the prediction of significant hyperbilirubinemia with sensitivity, specificity, positive predictive value and negative predictive value of 86%, 80%, 40%, 97%. In this study, ETCOc values were measured every 12th hourly during the first 72 hours of life. The ROC curve at 60 hours of age was the most prominently shifted upwards and to the left with the maximum area under the curve. This means that the ETCOc values at 60 hours of age is the most predictive of

significant hyperbilirubinemia. The cut-off point of 1.65 ppm at 60 hours of age provides reasonable high sensitivity, specificity, positive predictive value and negative predictive value (84.6%, 80.5%, 80.5% and 84.6%).

The ROC curve is a useful technique for describing a screening test and for ranking the merits of alternative tests, which was conducted to find the efficacy of measuring endtidal carbon monoxide for predicting significant hyperbilirubinemia. Like endtidal carbon monoxide, the carboxyhemoglobin value at 60 hours of age is the most predictive of significant hyperbilirubinemia. At the cut-off point of 1.32 ppm at 60 hours of age the sensitivity, specificity, positive predictive value and negative predictive value were 84.6%, 80.5%, 80.5% and 84.6%. The positive likelihood ratio was 4.34 and negative likelihood ratio was 0.19.

Schutzman DL et al, in his study showed Carboxyhemoglobin is useful in determining the etiology of severe hyperbilirubinemia in haemolytic process.¹³ Carboxyhemoglobin (COHB) values correlate well with pulmonary excretion of carbon monoxide for the estimation of bilirubin production.¹⁴ Endtidal Carbon monoxide measurements were found to correlate well with Carboxyhemoglobin measurements at different postnatal ages. The correlation between ETCOc and COHB is maximum with measurements done at 48 hours of life with a highly significant p value. There exists a mild correlation between TCB with ETCOc and TCB with COHB measurements at different post-natal ages, with a maximum correlation observed with measurements done at 72 hours of life.

Clinical impact of the study was with the ETCOc measurements authors were able to predict the development of significant hyperbilirubinemia in late preterm and term infants. But the prediction was maximum at the time when jaundice would also become clinically apparent for detection. This limits its clinical utility in practice as an early tool for prediction of subsequent hyperbilirubinemia. In This study, Carboxyhaemoglobin measurements by Masimo pulse oximetry proved to be an excellent alternative non-invasive tool compared to ETCOc measurements which warranted a tight seal with face mask. The carboxyhaemoglobin measurements by pulse oximetry could also be monitored in real time unlike ETCOc and hence would be more useful for bedside monitoring in NICU.

It is common in day today practice to see large number of subjects with risk factors who were discharged early after birth, land up with serum bilirubin values in exchange levels on follow up, particularly those with hemolytic jaundice. Hence, ETCOc and COHB could be used to predict the development of significant hyperbilirubinemia in all high risk neonates before discharge.

CONCLUSION

To conclude, the endtidal carbon monoxide (ETCOc) and carboxyhemoglobin (COHB) results in this study showed that increased levels in the early neonatal period was associated with prediction of subsequent significant hyperbilirubinemia.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Krishnan GR, Mangalabharathi S, Sajjid M, Ramya S. Endtidal carbonmonoxide and carboxyhemoglobin for prediction of significant hyperbilirubinemia in healthy Indian neonates >35 weeks of gestation. *Int J Contemp Pediatr* 2020;7:1225-31.