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Pediatrics 2006;118;276-279
DOI: 10.1542/peds.2005-3042

ARTICLE

The Contribution of Hemolysis to Early Jaundice in Normal Newborns

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVE. Neonatal jaundice is the result of an imbalance between bilirubin production and elimination, and our objective was to clarify the contribution of an increase in bilirubin production to hyperbilirubinemia in newborns.

METHODS. We measured the end-tidal carbon monoxide concentration corrected for ambient carbon monoxide concentration in 108 jaundiced newborns (total serum bilirubin level >75th percentile) and 164 control newborns in our well-infant nursery, for the first 4 days after birth.

RESULTS. Mean end-tidal carbon monoxide levels decreased in the control infants in the first 4 days but increased in the hyperbilirubinemic group. The differences between the jaundiced and nonjaundiced infants were statistically significant on all days.

CONCLUSIONS. Before hospital discharge, most infants with bilirubin levels >75th percentile are producing significantly more bilirubin than those with lower bilirubin levels. Because the ability of newborns to conjugate bilirubin is significantly impaired in the first few days, even a small increase in the rate of production can contribute to the development of hyperbilirubinemia. These data suggest that increased heme catabolism is an important mechanism responsible for hyperbilirubinemia in the first 4 days after birth.

www.pediatrics.org/cgi/doi/10.1542/peds.2005-3042

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Key Words
newborn infant, hyperbilirubinemia, jaundice, end-tidal carbon monoxide level, hemolysis

Abbreviations
CO—carbon monoxide
TcB—transcutaneous bilirubin
ETCOc—end-tidal carbon monoxide concentration corrected for ambient carbon monoxide concentration
TSB—total serum bilirubin
G6PD—glucose-6-phosphate dehydrogenase

Accepted for publication Jan 25, 2006

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Neonatal jaundice is the result of an imbalance between bilirubin production and elimination[1] and, although neonatal hyperbilirubinemia is very common, for many infants no identifiable pathologic cause of hyperbilirubinemia is found.[2,3] Bilirubin is the end product of the catabolism of heme; in the initial step of heme catabolism, carbon monoxide (CO) is formed, with 1 molecule of CO and bilirubin being formed for each molecule of heme degraded.[4,5] Therefore, measurement of end-tidal CO concentration corrected for ambient CO concentration (ETCOc) is a direct index of heme catabolism and bilirubin production,[4] and ETCOc values can indicate whether an increase in bilirubin production is contributing to hyperbilirubinemia. Our objective was to determine whether increases in heme turnover and bilirubin production contribute to hyperbilirubinemia in newborns in the first 4 days after birth.

METHODS

Between June 1 and October 31, 2001, after informed consent was obtained, we measured ETCOc for 108 jaundiced newborns and 164 control newborns in our well-infant nursery. All infants were at ≥36 weeks of gestation and well. The jaundiced infants were identified with a standard nursery protocol that was in place at that time. A transcutaneous bilirubin (TcB) measurement was obtained by the nursing staff, with a Minolta JM-102 jaundice meter (Minolta, Osaka, Japan), for any infant who appeared jaundiced. The JM-102 meter provides a TcB index. If the TcB index exceeded a certain level according to the infant's age, in hours (according to an established nursery protocol), then a total serum bilirubin (TSB) measurement was obtained. TSB concentrations were measured in the clinical laboratory with a diazo method (Synchron DxC-800; Beckman Coulter, Fullerton, CA). Infants whose TSB levels exceeded the 75th percentile for age, in hours,[6] constituted the study group (N = 108). The control group was a convenience sample of infants of similar age in the well-infant nursery. Infants qualified as control subjects if they were not jaundiced at the time of the ETCOc measurement or, if they were jaundiced, their TSB level did not exceed the 75th percentile. Infants were excluded as study or control infants if they were at ≤35 weeks of gestation or had respiratory distress or any condition necessitating transfer to the NICU. None of the control infants received phototherapy, whereas 16 (15%) of the jaundiced infants subsequently received phototherapy. ETCOc measurements were performed with a Natus CO-Stat end-tidal breath analyzer (Natus Medical, San Carlos, CA). We compared ETCOc values for these infants (N = 108) with those for the control population (N = 164). This study was approved by the hospital's human investigation committee.

RESULTS

The results are shown in Tables 1 and 2 and Fig 1. Mean ETCOc values decreased in the control group over the first 4 days but increased in the hyperbilirubinemic group, and the differences between the jaundiced and nonjaundiced infants were highly statistically significant on all days. For the jaundiced infants, 88 (81.5%) of 108 ETCOc values were above the mean and 28 (25.9%) of 108 were >2 SDs above the mean value for the control infants.

DISCUSSION

Measurement of ETCOc is a noninvasive, readily obtained measurement of bilirubin production in newborns, and we provide data for a normal population and a hyperbilirubinemic population of newborns, at ≥36 weeks of gestation, in the first 4 days of life. The hyperbilirubinemic infants (TSB concentration ≥75th percentile for age, in hours), as a group, had ETCOc values on each day that were significantly greater than those for the control population.

These infants were treated by private practitioners, and no established protocol was in place to measure the blood types of the mother and infant or to obtain blood cell counts and reticulocyte counts. Therefore, we cannot provide data on the incidence of ABO incompatibility or other potentially pathologic causes of hyperbiliru-

TABLE 1 **Demographic Data for the Jaundiced and Control Populations**

	Jaundiced (N = 108)	Control (N = 164)	P[a]
Mean birth weight, mean ± SD, g	3501 ± 473	3427 ± 514	.23
Gestational age, mean ± SD, wk	39.1 ± 1.5	39.1 ± 14	.84
Male, *n* (%)	53 (49.1)	85 (51.8)	.75
Breastfed (includes breast and formula), *n* (%)	91 (84.2)	133 (81.1)	.61
Race, *n* (%)[b]			
White	83 (76.9)	131 (79.9)	.66
Black	7 (6.5)	22 (13.4)	.11
Middle Eastern	13 (12.0)	4 (2.4)	.00
Asian, Hispanic, or unknown	5 (4.6)	7 (4.2)	.87

[a] Continuous data, 2-tailed *t* test; proportions, χ^2 test.
[b] According to the mother's description.

TABLE 2 **ETCOc Levels for Jaundiced and Control Infants and TSB Levels for Jaundiced Infants**

Age	TSB for Jaundiced Infants, mg/dL	ETCOc, ppm		*P*[a]
		Jaundiced	Control	
Day 1	8.0 ± 2.8	2.32 ± 0.61	1.99 ± 0.42	.000
Day 2	9.4 ± 2.0	2.37 ± 0.44	1.94 ± 0.51	.000
Day 3	13.3 ± 1.1	2.66 ± 0.36	1.66 ± 0.34	.000
Day 4–5	17.4 ± 2.6	2.99 ± 0.45	1.49 ± 0.33	.000

Values are mean ± SD. The majority of control infants did not have TSB measurements.
[a] Mann–Whitney *U* test for ETCOc levels, jaundiced versus control infants.

binemia, such as glucose-6-phosphate dehydrogenase (G6PD) deficiency. The racial demographic characteristics of the study and control populations are shown in Table 1. Because 77% of the jaundiced infants were white, there is no reason to suspect undiagnosed G6PD deficiency as an important (covert) cause of the hyperbilirubinemia. The jaundiced group did contain significantly more Middle Eastern infants and fewer black infants, and it is possible that some of those infants had G6PD deficiency; however, only 13 of 108 infants were Middle Eastern and, even if all had G6PD deficiency (an unlikely scenario), this would not explain the increase in bilirubin production in the rest of the jaundiced infants. The mean ETCOc for the jaundiced Middle Eastern infants was 2.41 ± 0.43 ppm, which was not different from the mean for the rest of the jaundiced group (2.43 ± 0.50 ppm). In previous studies of our newborn population, ~22% of infants who received phototherapy during their birth hospitalizations had Coombs' test-positive ABO incompatibility[7] but no pathologic cause of hyperbilirubinemia was identified for the majority of infants. Of the 108 jaundiced infants, only 16 (15%) subsequently received phototherapy.

We have no ready explanation for the apparent increase in bilirubin production over the first 4 days among the jaundiced infants. As expected, ETCOc values for the normal population declined during the same period.[8] In a large international study,[9] ETCOc measurements obtained at 30 ± 6 hours in a newborn population did not contribute significantly to the prediction of subsequent hyperbilirubinemia but did suggest that infants with subsequent hyperbilirubinemia had early evidence of increased heme turnover. If obtainable, serial ETCOc measurements on days 1 to 4 after birth might predict subsequent hyperbilirubinemia better than a single measurement.

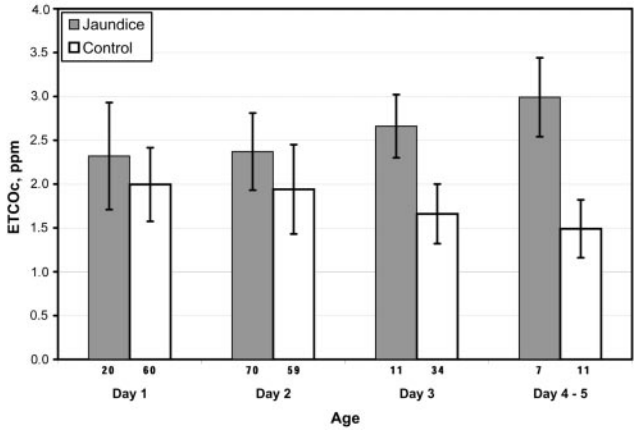

FIGURE 1
ETCOc values for jaundiced and control infants. Values shown are the mean ± SD for each age group. The numbers below the bars are the numbers of infants studied in each group.

It is difficult to obtain laboratory documentation of mild degrees of hemolysis among newborns. Such infants are unlikely to have decreasing hemoglobin concentrations, elevated reticulocyte counts, or abnormalities on peripheral smears. In any case, these laboratory tests are generally nonspecific and insensitive for newborns.[2,10] Measurements of blood carboxyhemoglobin levels with gas chromatography[11] (not available in clinical laboratories) and ETCOc provide direct measurements of heme turnover. Because the ability of newborns to conjugate and to clear bilirubin is significantly impaired in the first few days, even a small increase in the rate of bilirubin production can contribute to the development of significant hyperbilirubinemia. Bartoletti et al[12] found that 6 normal newborns with TSB levels >12 mg/dL and no apparent cause for jaundice had increased rates of CO excretion and, therefore, bilirubin production.

Because an increase in bilirubin production seems to be an important mechanism for the development of hyperbilirubinemia in the first 4 days after birth, an intervention aimed at decreasing bilirubin production would likely prevent most early neonatal jaundice. Tin-mesoporphyrin is a drug that inhibits the production of bilirubin and has been shown to be effective in both preventing and treating early neonatal hyperbilirubinemia.[13] Our data provide an explanation for its efficacy in this population (although it would prevent jaundice even if bilirubin production were not increased).

CONCLUSIONS

Before hospital discharge, most infants at ≥36 weeks of gestation with TSB levels in >75th percentile are producing significantly more bilirubin than those with lower TSB levels. This suggests that increased heme ca-

tabolism is an important mechanism responsible for hyperbilirubinemia in the first 4 days after birth.

ACKNOWLEDGMENTS

This study was supported by a grant from Natus Medical (San Carlos, CA). The company has discontinued production of the CO-Stat end-tidal breath analyzer.

We thank Thomas Newman, MD, MPH, and Michael Kaplan, MB, ChB, for advice and review of the manuscript.

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