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Capillary Blood Ketone Levels as an Indicator of Inadequate Breast Milk Intake in the Early Neonatal Period

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Objective To determine the utility of capillary blood ketone levels as an indicator of inadequate intake of breast milk in the early postnatal period.

Study design Levels of capillary blood beta-hydroxybutyrate (βOHB), the main ketone body in the blood, were measured with a bedside ketone meter in 585 full-term neonates aged 48-95 hours who were breastfed exclusively. Relationships between weight-loss percentage, blood sodium, glucose, pH, partial pressure of carbon dioxide, base-deficit levels, and βOHB levels were investigated. The diagnostic accuracy of βOHB for predicting excessive weight loss (weight loss ≥10% of birth weight) and hypernatremic dehydration (blood sodium level ≥150 mEq/L) was determined.

Results βOHB levels were correlated positively with weight-loss percentage and blood sodium levels and were correlated negatively with blood glucose levels. The diagnostic accuracy of βOHB was 0.846 (optimal cut off, 1.55 mmol/L; sensitivity, 80.9%, specificity, 74.0%) for predicting excessive weight loss and 0.868 (optimal cut off, 1.85 mmol/L; sensitivity, 94.3%; specificity, 69.9%) for predicting hypernatremic dehydration according to the area under the receiver operating characteristic curve. Multiple logistic analysis revealed that βOHB and weight loss percentage were the only independent predictors of hypernatremic dehydration. Increases in βOHB levels also were associated with worsening metabolic acidosis and hypocapnia.

Conclusion High βOHB levels were associated with inadequate intake of breast milk in the early postnatal period. The use of bedside capillary blood ketone levels may be clinically useful as an indicator of dehydration, energy depletion, and acid-base imbalance in breastfeeding infants in the early postnatal period. *(J Pediatr 2017;191:76-81).*

Because breast milk is the optimal nutrition for neonates, exclusive breastfeeding is recommended for the first 6 months after birth.[1-4] To promote and support exclusive breastfeeding, the World Health Organization and United Nations Children's Fund launched the Baby-Friendly Hospital Initiative and recommended the Ten Steps to Successful Breastfeeding.[5,6] Included in these steps is avoidance of supplementary feedings unless medically indicated[7] because early supplementation interferes with the lactation process and is associated with early cessation of breastfeeding.[8-12] However, inadequate intake of breast milk may lead to excessive weight loss and hypernatremic dehydration (HD).[13,14] To avoid these complications, weight loss >10% of birth weight is accepted as an indication for supplementation.[15,16] However, a recent large cohort study demonstrated that >25% of neonates from cesarean deliveries who were breastfed exclusively had lost ≥10% of their body weight by 72 hours.[17] Supplementation of all these neonates may be unnecessary because HD is rare in this period.[18] Blood sodium is an accurate marker of dehydration, but bedside micromethods for determination of blood sodium are not readily available. Therefore, a reliable, facile indicator of inadequate breast milk intake is needed.

Ketone bodies are produced by the liver from fatty acids when nutrient intake is insufficient. Under conditions of limited glucose supply, ketone bodies are an important alternative fuel for the brain, and neonates actively produce and use ketone bodies.[19,20] Increases in plasma ketone levels in breastfed neonates have been correlated with excessive weight loss.[21] However, laboratory measurement of plasma ketones is expensive, time-consuming, and may require a substantial amount of blood. Hence, adaptation of ketone measurement for clinical use has been challenging.

Quantitative bedside testing of beta-hydroxybutyrate (βOHB) with very small blood samples is now available for monitoring ketone levels in patients with diabetes and may be feasible for use in neonates. In the current study, we used this device to measure capillary blood βOHB levels in neonates who were breastfed exclusively during the early postnatal period to evaluate the utility of this method for identifying inadequate intake of breast milk.

βOHB	Beta-hydroxybutyrate
HD	Hypernatremic dehydration
pCO_2	Partial pressure of carbon dioxide
ROC	Receiver operating characteristic

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Methods

This study included 585 neonates who were born at Toyama Prefectural Central Hospital (Toyama, Japan) from March 2012 to June 2015. Inclusion criteria were singleton; full-term birth (37-41 weeks of gestation), birth weight between the 10th and 90th percentiles (according to Japanese population standards), exclusive breastfeeding (breast milk only, with no other fluids or solids) at the time of blood sampling, and Apgar score of >7 at 1 minute. Neonates of mothers with diabetes, hypertension, or who were using corticosteroids or ritodrine during the last 4 weeks of pregnancy were excluded. All neonates were breastfed on demand. Body weight was measured daily between 9:00 a.m. and 11:00 a.m. with a single electronic digital scale. The percentage of weight loss was calculated with the following formula: 100 × (birth weight − present weight) / birth weight.

After each weight measurement, 100 µL of capillary blood was obtained by heel prick and transferred to heparin-coated tube (safe CLINITUBES, Radiometer, Copenhagen, Denmark). Capillary blood βOHB levels were measured with a bedside ketone meter (required blood volume, 1.5 µL; Precision Xceed, Abbott, Tokyo, Japan). Blood sodium, glucose, pH, partial pressure of carbon dioxide (pCO_2), and base deficit levels were determined with a blood gas and electrolyte analyzer (ABL 800; Radiometer, Copenhagen, Denmark). All samples were obtained from neonates aged 48-95 hours during their perinatal hospital stay. We chose this time interval because the vast majority of exclusively breastfed neonates experience a weight nadir during this period.[17] Neonates were recruited randomly for this study. In addition, we included most neonates with weight loss ≥10%, because they were required to have clinical examination for dehydration, hypoglycemia, jaundice, or other conditions that could interfere with breastfeeding.

Statistical Analyses

Bivariate analysis between weight-loss percentage, blood levels of sodium, glucose, pH, pCO_2, base-deficit, and blood βOHB levels were tested with the Spearman rank correlation coefficient. The χ^2 test or Fisher exact test was used for statistical comparisons of frequencies between categorized βOHB levels. Receiver operating characteristic (ROC) curves were used to determine the diagnostic accuracy of βOHB for predicting excessive weight loss (weight loss ≥10% of birth weight) and HD (blood sodium ≥150 mEq/L). The optimal cut-off point was determined via the Youden index (sensitivity + specificity − 1). The association of βOHB level with HD was examined by stepwise backward multiple logistic regression analysis, controlling for the following potential confounders: mother's age, parity, mode of delivery, sex, gestational age, birth weight, and time after birth. Results were expressed as adjusted ORs with 95% CIs. To identify independent factors associated with βOHB level, stepwise multiple regression analysis was performed. A two-sided $P < .05$ was considered statistically significant. All statistical analyses were conducted with SPSS software, version 22 (IBM, Tokyo, Japan). Hypoglycemia was defined as blood glucose <47 mg/dL in this study.[22-24] This study was approved by our institutional ethics committee, and all parents provided written informed consent.

Results

Demographic data of the study population are summarized in the **Table**. We obtained a total of 585 data points from each neonate for analyses of blood sodium, glucose, and βOHB levels. Among them, a total of 488 data points were available for analyses of blood base-deficit, pH, and pCO_2 levels.

A strong positive correlation was determined between βOHB levels and weight-loss percentages (r = 0.740; $P < .001$) (**Figure 1**, A). Excessive weight loss was observed in 4.1%, 34.5%, 66.9%, and 89.6% of neonates with βOHB levels <1.0 mmol/L, 1.0-1.9 mmol/L, 2.0-2.9 mmol/L, and ≥3.0 mmol/L, respectively ($P < .01$, $P < .01$, $P < .01$, respectively, between successive βOHB categories). The diagnostic accuracy of βOHB for predicting excessive weight loss according to the area under the ROC curve was 0.846 (95% CI, 0.815-0.876; $P < .001$) (**Figure 1**, B). The optimal cut-off point of βOHB was 1.55 mmol/L with a sensitivity of 80.9% and a specificity of 74.0%.

There was a strong positive correlation between βOHB and blood sodium levels (r = 0.703; $P < .001$) (**Figure 1**, C). HD was found in 35 neonates. HD was observed in 0.0%, 2.6%, 12.0%, and 27.1% of neonates with βOHB levels <1.0 mmol/L, 1.0-1.9 mmol/L, 2.0-2.9 mmol/L, and ≥3.0 mmol/L, respectively ($P = .04$, $P < .01$, $P = .02$, respectively, between successive βOHB categories). The diagnostic accuracy for predicting HD according to the area under the ROC curve was 0.868 (95% CI 0.822-0.915; $P < .001$) for βOHB and 0.886 (95% CI 0.837-0.936; $P < .001$) for weight-loss percentage (**Figure 1**, D). The optimal cut-off points of βOHB and weight loss percentage were 1.85 mmol/L (sensitivity, 94.3%; specificity, 69.9%) and 10.85% (sensitivity, 82.9%; specificity 83.1%), respectively. Results of stepwise backward multiple logistic regression analysis determined that βOHB (OR 2.63; 95% CI, 1.64-4.23; $P < .001$) and weight-loss percentage (OR 2.75; 95% CI, 1.82-4.17; $P < .001$) were independent predictors of HD. Blood glucose level, mother's age, parity, mode of delivery,

Table. Characteristics of the 585 neonates and their mothers in the study

Characteristics	Mean (SD) or n (%)
Mother's age, y	32.6 (5.0)
Primiparous/multiparous	343 (59)/242 (41)
Vaginal/cesarean delivery	428 (73)/157 (27)
Sex	
Female/male	277 (47)/308 (53)
Gestational age, wk	39.4 (1.1)
Birth weight, g	3051 (272)
Neonates categorized by weight loss	
<7.0%	121 (21)
≥7.0% and <10.0%	244 (42)
≥10%	220 (37)