Prevalence and Determinants of Hyperglycemia in Very Low Birth Weight Infants: Cohort Analyses of the NIRTURE Study

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Objectives To investigate the prevalence and determinants of hyperglycemia in the preterm population, as part of the Neonatal Insulin Therapy in Europe (NIRTURE) Trial.

Study design We conducted prospective cohort analyses of continuous glucose monitoring data from control infants participating in an international randomized controlled trial. Data were collected from 188 very low birth weight infants (<1500 g).

Results In the first week of life, 80% of infants had evidence of glucose levels >8 mmol/L, and 32% had glucose levels >10 mmol/L >10% of the time. Independent risk factors for hyperglycemia included increasing prematurity, small size at birth, use of inotropes, lipid infusions, and sepsis. There was a lack of association between rate of dextrose infused and risk of hyperglycemia.

Conclusion The prevalence of hyperglycemia in the very low birth weight infant is high, with marked variability in prevalence between infants, not simply related to rates of glucose infused, but to other potentially modifiable risk factors. *(J Pediatr 2010;157:715-9)*.

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Retrospective studies have reported that high glucose levels are common in the preterm infant and are an independent risk factor for increased mortality[1,2] and morbidity rates.[3-6] However, the prevalence and determinants of high glucose levels remain poorly defined. Earlier studies were retrospective and dependent on the use of infrequent blood glucose levels that were taken for clinical reasons[7] and were potentially biased by the severity of illness. The use of continuous glucose monitoring (CGM), as part of the Neonatal Insulin Replacement Therapy in Europe (NIRTURE) Trial, provided detailed data on glucose control in a cohort of very low birth weight infants (VLBW; birth weight <1500 g).[8] The data from CGM was blinded to clinicians who were involved in clinical care, so did not affect management of glucose control. The accuracy of the CGM in the preterm population was reported.[9] We therefore used these data to investigate the prevalence and determinants of high glucose levels in the first week of life in high-risk preterm infants.

Methods

The subjects were part of the NIRTURE Trial (ISRCTN78428828). This was an international multicenter randomized controlled study investigating the role of early insulin in VLBW infants.[8] Ethical and regulatory authority approval (Eudract No 2004-002170-34) were obtained for each center, and the protocol is in the public domain.[10] Infants were recruited from 8 European centers between February 2005 and August 2007. Written informed parental consent was obtained before recruitment, which was within 24 hours of birth. Exclusion criteria

CGM	Continuous glucose monitoring
CRIB	Critical risk index for babies
EDD	Expected date of delivery
NIRTURE	Neonatal Insulin Therapy in Europe
OR	Odds ratio
PROM	Prolonged rupture of membranes
SDS	Standard deviation score
SG	Sensor glucose
VLBW	Very low birth weight

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included maternal diabetes mellitus and major fetal congenital abnormalities. Infants were observed to the expected date of delivery (EDD). The trial was monitored and coordinated by the British Society of Paediatric Endocrinology and Diabetes Clinical Trials Unit in Cambridge in accordance with international guidelines.[11]

Only control subjects with CGM data were included in the analyses (n = 188), but they were representative of the cohort as a whole.[8] The infants all received standard clinical treatment, with hyperglycemia defined as blood glucose levels >10 mmol/L on at least 2 occasions, initiating a clinical decision as to whether to reduce the rate of dextrose infusion or to start a sliding scale intravenous insulin infusion. CGM data were not available in real time and therefore did not influence clinical care. There were occasions when the CGM required replacement during the 7-day study period because of loss of signal, but there were no reports of infection or inflammation at the site of sensor insertion.

A subcutaneous glucose sensor was inserted into the lateral thigh within 24 hours of birth, from which continuous measurements were recorded for 7 days. Use of the CGM (Medtronic, Minneapolis, Minnesota) in the preterm infant has been described.[9] In essence, the device is composed of a disposable glucose oxidase-based platinum electrode sensor that is inserted subcutaneously. This sensor catalyzes interstitial glucose, and this is converted to an averaged glucose value every 5 minutes. Glucose values outside the range of 2.2 to 24.0 mol/L (40-430 mg/dL) are recorded as <2.2 mmol/L (40 mg/dL) or >24 mmol/L (430 mg/dL), respectively. The monitor was calibrated at least 3 times daily with a blood sample measured with the method normally used on each unit for clinical management of glucose, using a combination of arterial, venous, or capillary samples.

The CGM data were downloaded at completion of the 7-day study period. All CGM data were reviewed to identify any periods when the sensor was failing but was still recording, and these data points were removed from the analyses. In total, a period of 3.0 days (0.2% of the data) were removed from the analyses, representing a proportion of data from 9 babies (median, 8.8 hours of data; range, 2.3-11.8 hours of data). The total CGM data used in the analyses represented 1254 days of data. The mean (SD) duration of CGM recordings was 156.2 (29) hours (6.5 days).

Analyses

Patterns of high glucose levels were determined from the CGM data. Hyperglycemia was defined at a selection of thresholds (at least 1 sensor glucose reading): >8 mmol/L, >10 mmol/L, >15 mmol/L, and >20 mmol/L. The prevalence of hyperglycemia for each subject was defined as the percentage of the total CGM monitoring time spent higher than the defined threshold. These definitions do not provide exclusive groups, but were selected because they classify hyperglycemia in terms of hyperglycemic exposure. Variables explored were previously reported antenatal and postnatal risk factors for poor clinical outcomes and included gestational age, birth weight standard deviation score (SDS), placental insufficiency (defined as documented ultrasound evidence of abnormal blood flow in the umbilical artery), prolonged rupture of membranes (PROM >24 hours), proven infection (clinical signs combined with positive blood or cerebrospinal fluid culture test results), and suspected infection (clinical concerns warranting treatment with antibiotics for >48 hours, but with negative culture test results). Nutritional intake was calculated as mean dextrose, protein, and lipid infused and oral milk intake. The Clinical Risk Index for Babies (CRIB) score was calculated for all infants as a marker of illness severity on day 1. This score has been validated in infants <31 weeks gestation or <1500 g who are admitted to neonatal intensive care.[12] Variables that were not normally distributed were examined and converted into categorical variables.

Percent of time hyperglycemic for each of the thresholds of hyperglycemia was not normally distributed. Before further investigation of determinants, hyperglycemia was classified in what was considered clinically significant binary variables: (1) early onset as onset of hyperglycemia (>10 mmol/L) within 48 hours of age; (2) mild hyperglycemia as >10% time >8 mmol/L; (3) moderate hyperglycemia as >10% time >10 mmol/L; (4) severe hyperglycemia as >10% time >15 mmol/L; and (5) uncontrolled hyperglycemia as any time >20 mmol/L. The value of 10% of study time is equivalent to an average of approximately 15 hours. Logistic regression was performed initially, including each variable in addition to gestational age and birth weight SDS (with SPSS software version 15.0; SPSS Inc., Chicago, Illinois). Then further models were investigated by using multivariate logistic regression, including any variables that were significant in the initial analyses ($P < .05$) and gestational age and birth weight SDS.

Results

The characteristics of this cohort of 188 infants are shown in **Table I**. When the data for all infants were combined, the prevalence of each of the thresholds of hyperglycemia remained relatively stable for the 7-day study period (**Figure 1**; available at www.jpeds.com). However, there was significant variability in the prevalence of hyperglycemia in infants. Some infants did not experience any periods with glucose levels >10mmol/L, whereas other infants spent prolonged periods with sensor glucose readings >10 mmol/L (**Figure 2**; available at www.jpeds.com). The numbers of infants reaching the thresholds for each defined level of hyperglycemia are shown in **Table II** (available at www.jpeds.com). Glucose levels >8 mmol/L occurred in 80% of infants, glucose levels >10 mmol/L occurred in 57% of infants, glucose levels >15 mmol/L in 23% of infants, and 9% of infants had at least 1 glucose reading >20 mmol/L. Classification in what was considered clinically significant periods of high glucose levels demonstrated: early onset hyperglycemia was present in 29% of infants, mild hyperglycemia was present in 49% of infants, moderate